A.M.A. Archives of
OPHTHALMOLOGY

MARCH 1956
VOLUME 55 NUMBER 3

The Facility of Aqueous Outflow
Bernard Becker and Marguerite A. Constant

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Joseph W. Hallett, Irving H. Leopold, and Susan Inwald

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Otto Lowenstein

Critical Fusion Frequency in Retrobulbar Neuritis
Yoshi Kurachi and Daizo Yonemura

Ocular Axes and Meridians During Oblique Oculorotations
Arthur Linksz

A Bibliography of the History of Ophthalmology
Charles Snyder

Visual Acuity Decrease at Various Illuminations and Role of Reading
Curt Berger

Diseases of the Uveal Tract
F. Phinizy Calhoun Jr.

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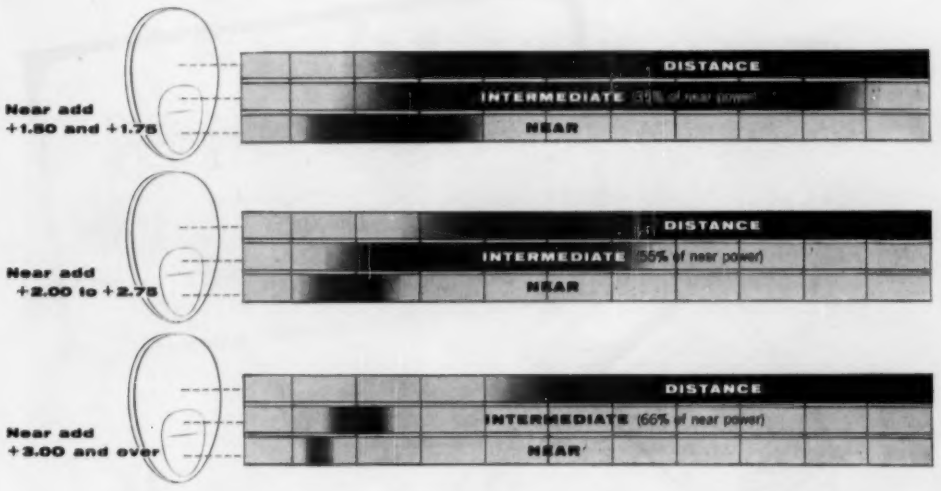

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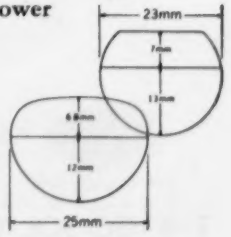

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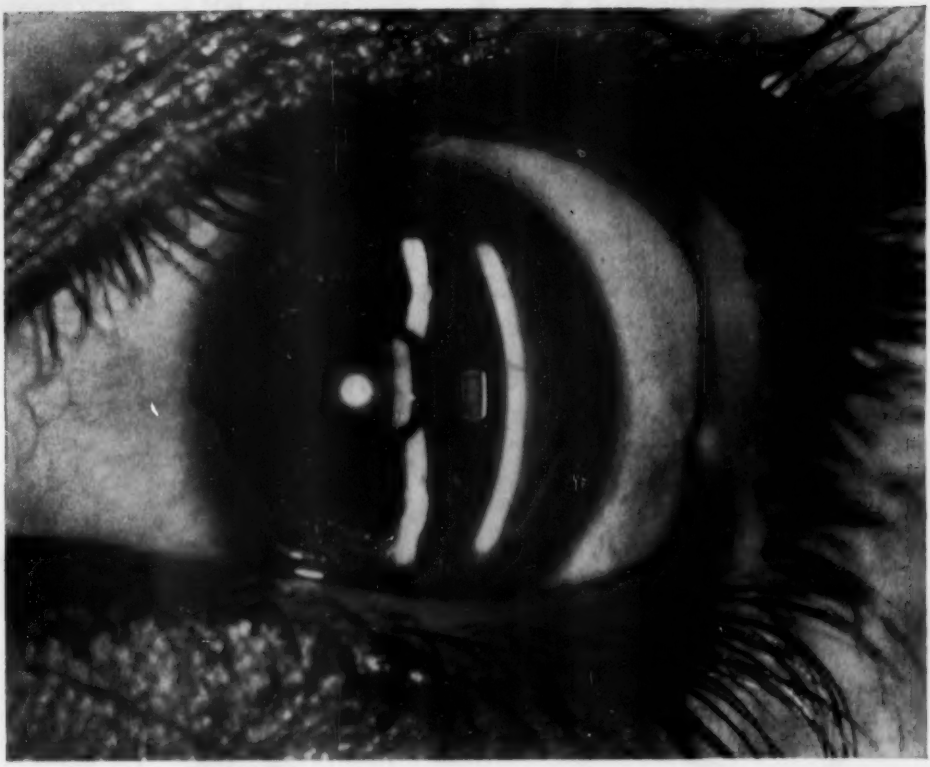

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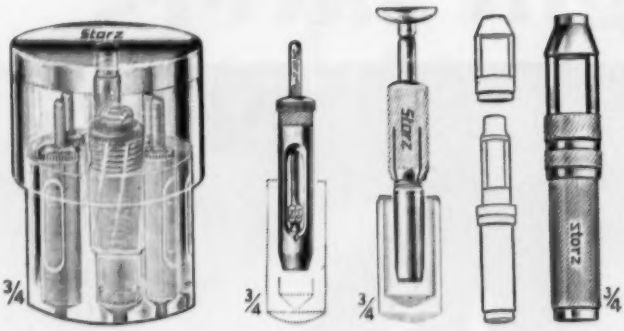

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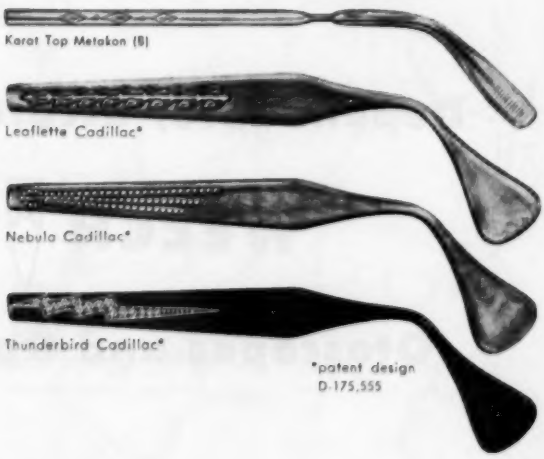

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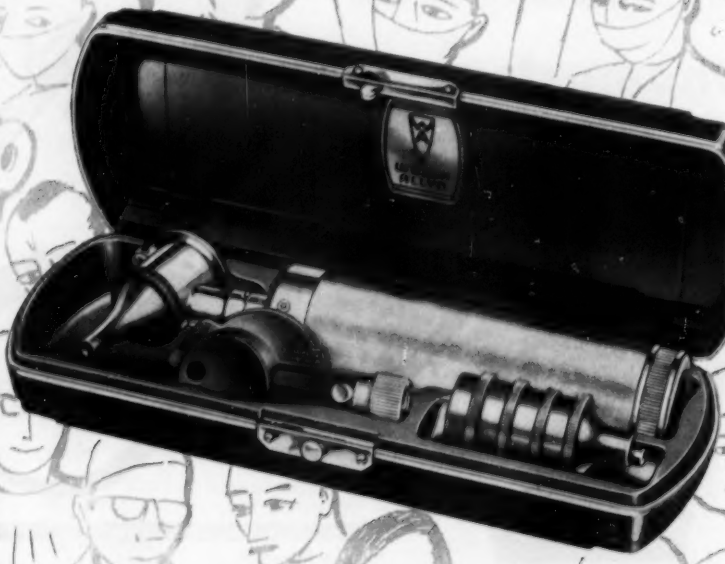

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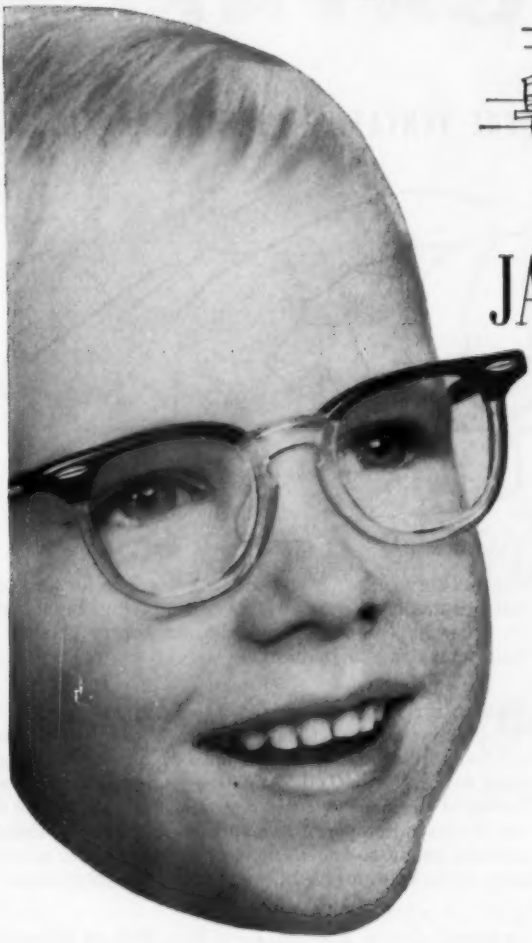

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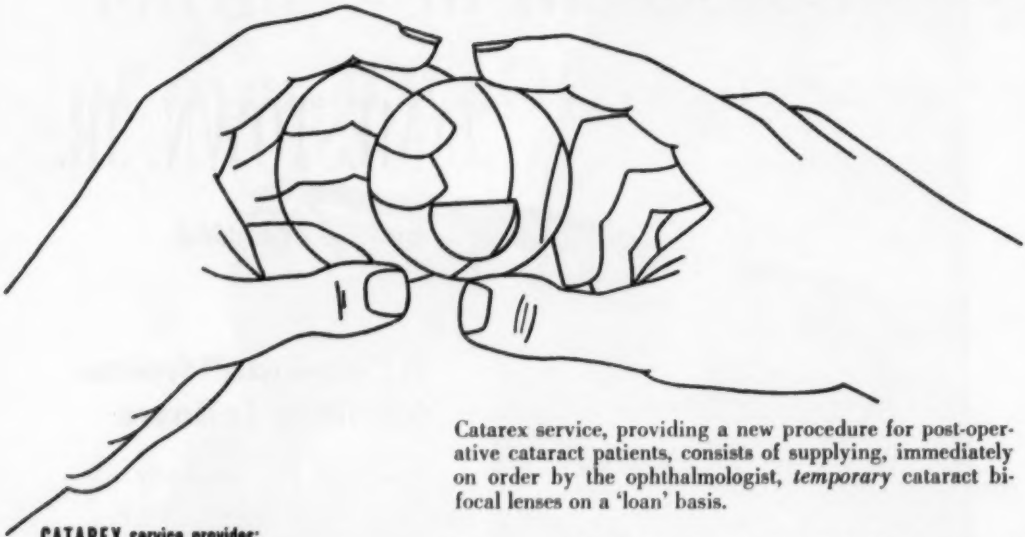

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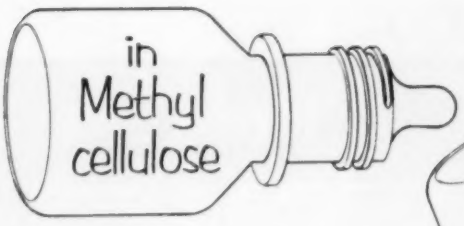

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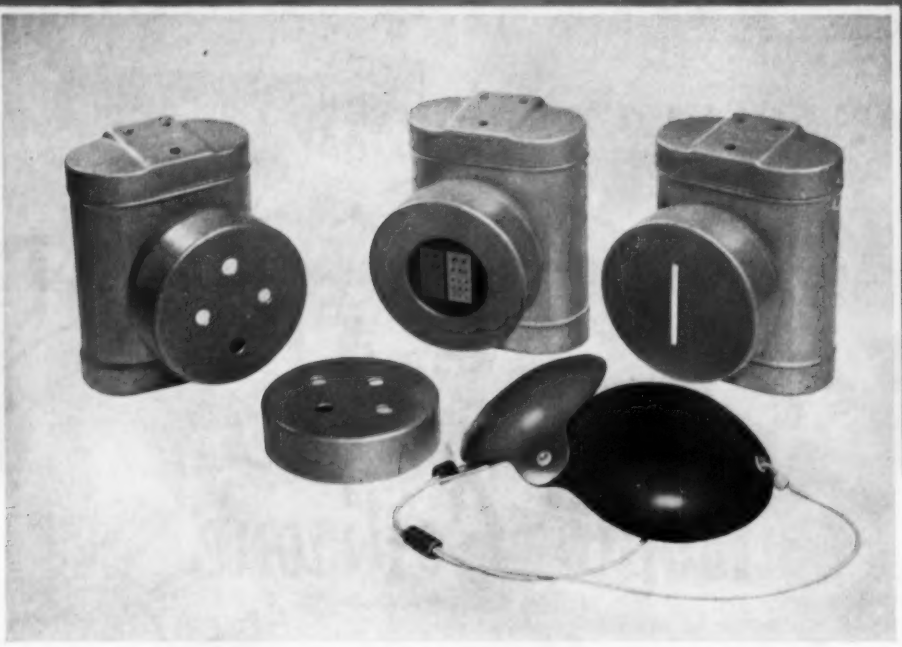

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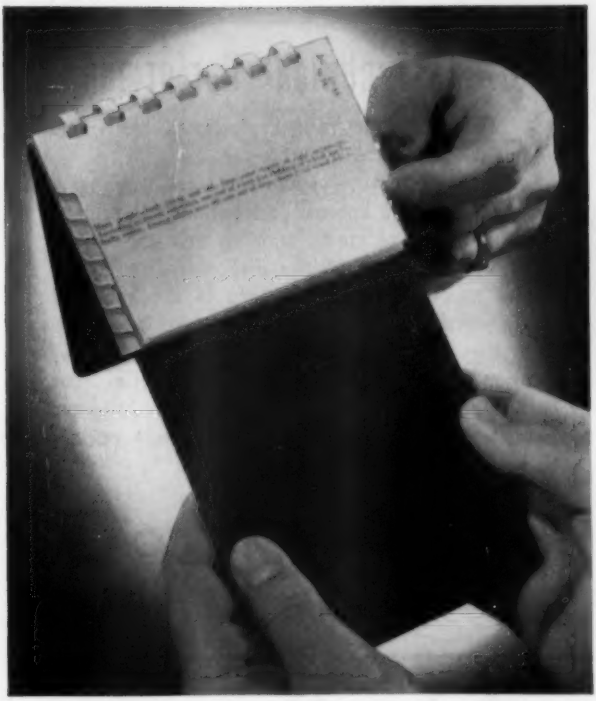

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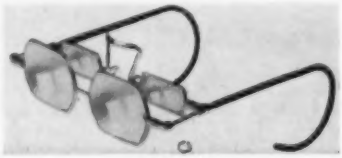

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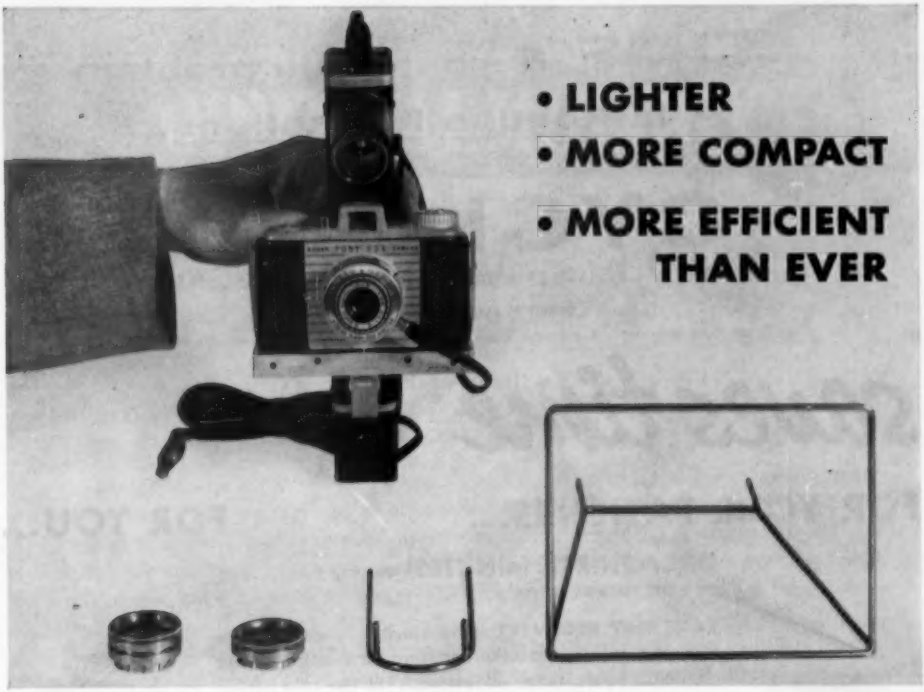

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The Facility of Aqueous Outflow

A Comparison of Tonography and Perfusion Measurements In Vivo and In Vitro

BERNARD BECKER, M.D.
and
MARGUERITE A. CONSTANT, Ph.D., St. Louis

The perfusion methods of Bárány [1] and Grant [2] provide a direct experimental approach to the measurement of aqueous outflow in the enucleated eye. When the method is applied to human eyes, opportunities are afforded for comparing in vitro values for facility of outflow with those calculated from tonographic tracings. Such comparison has demonstrated remarkably similar average values for the two populations of normal human eyes.[3]

The fortunate finding that tonography could be applied to rabbit eyes * permitted comparing the in vitro and in vivo methods in this experimental animal. Furthermore, this comparison could be made more precise by examining the same eye before and after enucleation, thus avoiding individual variation. In addition, the intermediary step before enucleation of perfusion in the living animal has been utilized. The data obtained by such cannulation in the living eye provided additional values for intraocular pressure (P_0), as well as the facility of outflow (C). It is the purpose of this report to compare tonographic tracings and perfusion in vivo and in vitro on the eyes of rabbits. It has also been possible to apply all three methods to a limited number of human eyes just prior to and immediately following enucleation.

METHODS

Male rabbits (Haskins Rabbitry, St. Louis), weighing 2-3 kg., were used. Tonography was carried out on human and rabbit eyes as described previously,[4] using an electronic tonometer and a Leeds & Northrup recorder. The 1955 calibration tables of Friedenwald [5] were used for

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From the Department of Ophthalmology, Washington University School of Medicine and the Oscar Johnson Institute (Dr. Becker).

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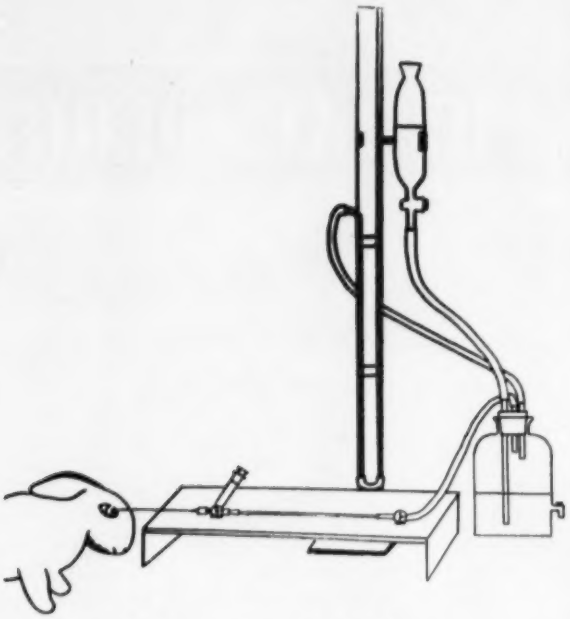

Fig. 1.—Schematic representation of perfusion apparatus.

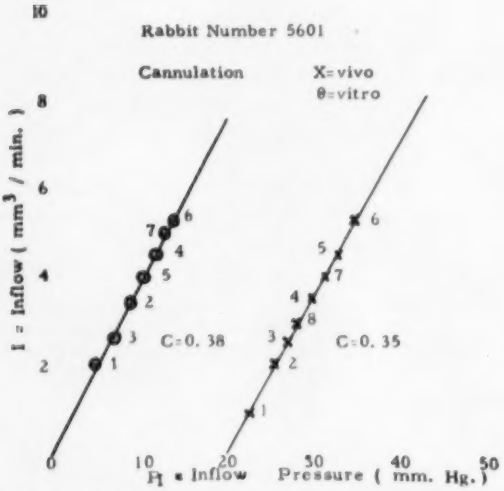

Fig. 2.—Comparison of perfusion measurements in vivo and in vitro in a representative rabbit eye.

determining values for intraocular pressure (P_o) and for computing values for facility of outflow (C). Perfusion in vitro was performed by a modification of the method described by Bárány.[1] Isotonic saline at pH 7.0 was forced through a horizontal 0.2 ml. pipet calibrated in 0.001 ml. divisions by a pressure system that could be maintained at any level between 0 and 40 mm. Hg. The pipet was connected to the eye by means of polyethylene tubing (Fig. 1) and a 24-gauge stainless steel or platinum cannula. During the infusion procedure, the freshly

enucleated eyes were kept in a bed of cotton moistened with isotonic saline. Additional saline was dropped on the cornea at frequent intervals. At the time of enucleation, efforts were made to obtain 2-3 mm. lengths of optic nerve and to dissect conjunctiva close to the limbus as atraumatically as possible. In contrast to Bárány's constant pressure method, efforts were directed toward varying the pressure and measuring the rate of inflow (I) in cubic millimeters per minute at various pressure levels (P_I). The same procedure was applied to the eye of the heparinized living animal, either under local tetracaine or general anesthesia (pentobarbital [nembutal] or urethan).

It is evident that in the living animal eye subjected to perfusion the facility of outflow (C) is defined as follows:

$$C = \frac{I}{P_I - P_o} \tag{1}$$

where I = rate of saline inflow (cu. mm/min.)
P_I = inflow pressure (mm. Hg).
P_o = intraocular pressure before cannulation (mm. Hg).

When Equation (I) is written in the form

$$I = C\,(P_I - P_o) \tag{2}$$

it is apparent that plotting the data for inflow (I) versus inflow pressure (P_I) should result in a straight line with slope C, the facility of outflow. Furthermore, when $I = 0$, $P_I = P_o$ and, therefore, the X-intercept of the straight-line plot provides an estimate of P_o, the intraocular pressure before cannulation. At a given facility of outflow, the extrapolated value of P_o, and particularly its excess over the episcleral venous pressure, P_V, is a measure of the rate of aqueous secretion, much as it is in tonography. Thus,

$$F = C\,(P_o - P_V) \tag{3}$$

where F = rate of aqueous secretion (cu. mm/min.).
C = facility of outflow (cu. mm/min/mm. Hg)
P_o = intraocular pressure in the undisturbed eye (mm. Hg)
P_V = episcleral venous pressure (mm. Hg)

TABLE 1.—*Perfusion Versus Tonography* *

(Rabbits)

	Tonography	Perfusion	
		Vivo	Vitro
P_o	20	19	..
C	0.33	0.35	0.37
(No. eyes)	(90)	(53)	(40)

* P_o = intraocular pressure (mm. Hg).
C = facility of outflow.

One of the principal difficulties encountered with perfusion in vivo was the occurrence of spontaneous or induced cessation of secretion. This represented itself as a shift to the left of the straight-line plot of I versus P_I from an intercept at P_o down to an intercept at 9 or 10 mm. Hg (i. e., episcleral venous pressure). This change occurred without significant alteration in the slope of the straight line (i. e., C was not altered). Similar suppression of secretion by cannulation in vivo was evident in the data on dogs of Friedenwald and Pierce [6] and has been noted also in similar in vivo experiments in rabbits by Bárány.† The mechanism of this inhibition of secretion is under study. Factors favoring the induced failure of the secretory process include (1) sudden alterations in infusion pressure, (2) excessive trauma at the time of cannulation, (3) the use of albino animals, (4) deep anesthesia, and (5) prolonged perfusion.

In the enucleated eye, if the intraocular pressure is zero, Equation (2) may be simplified to

$$I = C \times P_I \tag{4}$$

This is the formulation used by Bárány [1] and by Grant.[2] In enucleated eyes it is important to correct the flow rate for the difference in viscosity of water at the temperature of the in vitro experiment from that at 37 C.[2]

Examples of the in vivo and in vitro data obtained for the rabbit eye were plotted in the above manner in Figure 2. At each pressure, repeated readings were taken of the inflow rate until a constant value was reached. The plotted points were numbered in the chronologic order of measurement.

† Bárány, E.: Personal communication, 1955.

RESULTS

In Table 1 are presented the average normal rabbit values for intraocular pressure (P_0) measured by tonography and by perfusion in vivo. Mean values for facility of outflow (C) determined by tonography and perfusion both in vivo and in vitro are also tabulated for comparison. It is apparent that the agreement is remarkably good for these large populations of normal rabbit eyes. Since episcleral venous pressure in the rabbit eye averages 9 mm. Hg, the average value for intraocular pressure (19 mm. Hg) and facility of outflow (0.35) indicate an average normal rate of flow of 3.5 cu. mm/min. in this size of rabbit eye. Such a rate of

TABLE 2.—*Comparison of in Vivo and in Vitro Estimates of Facility of Outflow and Intraocular Pressure in Rabbits* *

Vivo		Vitro	Tonography	
P_0	C	C	P_0	C
22	0.35	0.37	22	0.32
16	0.30	0.32	17	0.29
18	0.41	0.40	15	0.32
25	0.38	0.39	21	0.37
15	0.45	0.42	15	0.37
19	0.23	0.30	21	0.24
15	0.30	0.27	21	0.24
25	0.45	0.50	17	0.35
15	0.27	0.35	13	0.30
20	0.44	0.51	17	0.47
19	0.14	0.19	21	0.18
24	0.23	0.25	24	0.30
19	0.21	0.26	21	0.24
15	0.24	0.21	17	0.22
20	0.45	0.57	17	0.47
16	0.44	0.55	15	0.43
11	0.54	0.50	10	0.45
22	0.40	0.55	21	0.45
12	0.35	0.33	13	0.35
10	0.34	0.35	10	0.34
24	0.22	0.22	29	0.24
20	0.36	0.26	27	0.30
19	0.21	0.36	24	0.35
20	0.40	0.45	20	0.45
20	0.41	0.43	17	0.33
20	0.42	0.45	20	0.37
16	0.41	0.44	13	0.40
18	0.23	0.30	24	0.30
Average 18	0.34	0.37	19	0.33
S. D. ±3.7	±0.10	±0.11	±4.8	±0.09

* Vivo = perfusion in the living animal.
Vitro = perfusion in the enucleated eye.
P_0 = intraocular pressure in the undisturbed eye.
C = facility of outflow.

flow is in excellent agreement with the estimates of Kinsey and Palm [7] and Becker [8] obtained from turn-over measurements of test substances (i. e., 3-4 cu. mm/min.)

Of even greater interest was the comparison of values in the 28 rabbit eyes in which all three methods could be carried out successfully on the same eye (Table 2). Considering the errors of measurement inherent in tonography, as well as in perfusion experiments on rabbits, the facility results obtained by all methods are quite similar. The average difference among methods amounts to only 12%-15%.

It has proved possible to carry out tonography and perfusion measurements in vivo on four human eyes prior to enucleation. Three of these eyes were enucleated

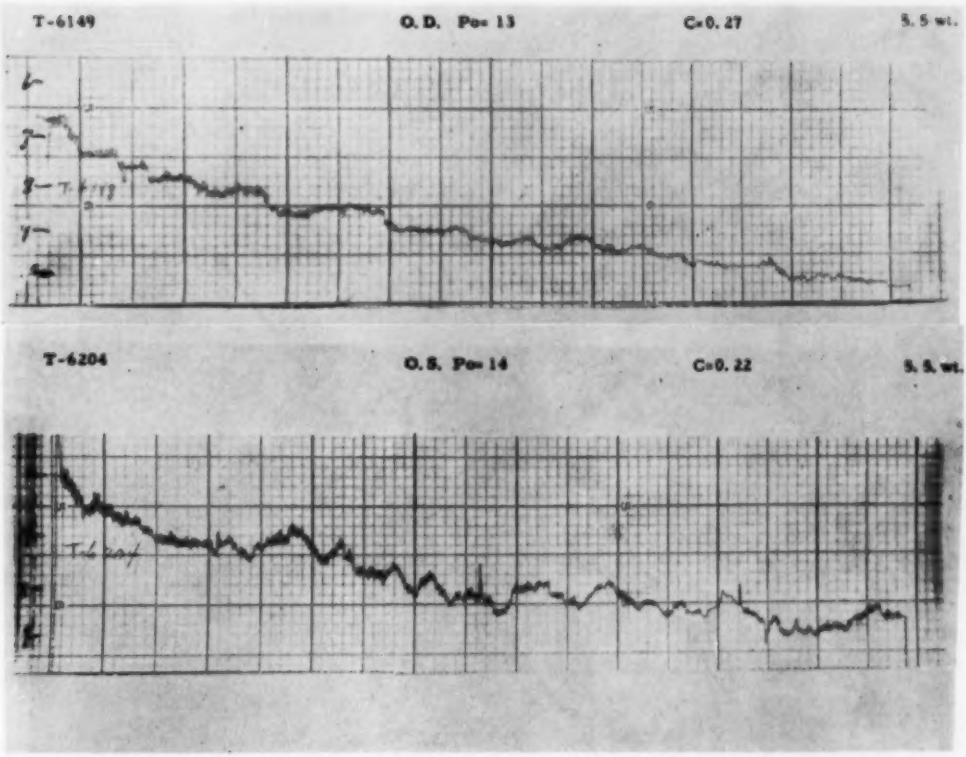

Fig. 3.—Tonographic tracings of human eyes prior to enucleation. Upper tracing: right eye of E. R., a 71-year-old white woman. Lower tracing: left eye of J. T., a 52-year-old white man.

TABLE 3.—*Perfusion Versus Tonography* *

	(Human)		
		Perfusion	
Patient	Tonography	Vivo	Vitro
E. R.			
P_o	13	16	..
C	0.27	0.26	0.29
J. T.			
P_o	14	15	..
C	0.22	0.21	0.24
E. E.			
P_o	12	13	..
C	0.20	0.21	0.23
H. H.			
P_o	17	16	..
C	0.25	0.24	0.26

* P_o = intraocular pressure (mm. Hg) in undisturbed eye.
C = facility of outflow.

for malignant melanomas, and one normal eye was removed as part of an exenteration of the orbit for carcinoma. These experiments were performed by both methods, using only local tetracaine for anesthesia. Immediately following enucleation the in vitro perfusion experiments were completed. In Figure 3 are duplicated the tonographic tracings of the first two patients. The upper tracing in Figure 3 is of

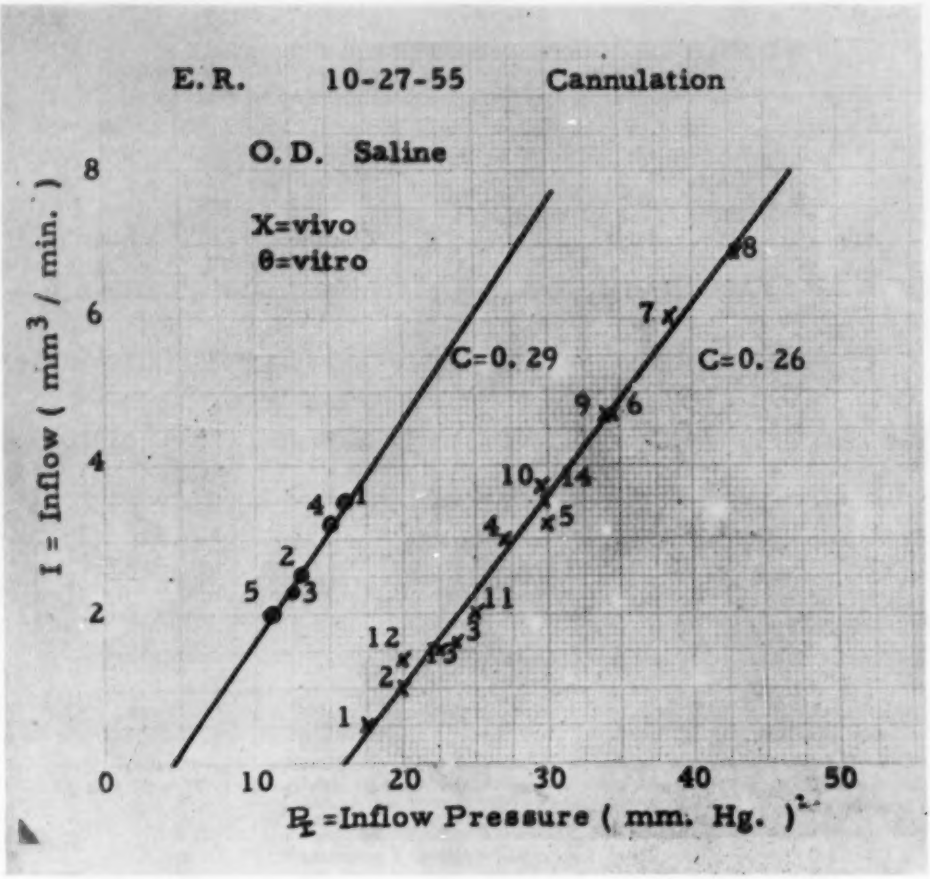

Fig. 4.—Perfusion data in vivo and in vitro of Patient E. R. (compare with upper tracing, Fig. 3).

the right eye of E. R., a 71-year-old white woman, and the lower tracing, of the left eye of J. T., a 52-year-old white man. In Figures 4 and 5 are plotted the inflow versus the inflow pressure data for each of these eyes, both in vivo and in vitro. The pertinent values for facility of outflow and intraocular pressure in both eyes, as well as those of a third eye, with malignant melanoma (E. E., a 59-year-old white man), and the one normal eye (H. H., a 45-year-old white man) are summarized in Table 3.

COMMENT

The clinical use of tonography has afforded remarkable opportunities for the diagnosis and regulation of the glaucomas.‡ The experimental use of repeated tonograms has provided estimates of the rate of aqueous flow and its alterations. Values for rabbit eyes obtained by this means have been in reasonable agreement with those derived from alterations in chemical composition[14] and from tracer studies.§ The present findings of agreement of in vivo determinations which involve

‡ References 9-13.

§ References 7 and 8.

such different variables as tonography and cannulation provide convincing additional evidence for the validity of tonographic estimates. At least errors inherent in the methods do not appear to be of measurable significance when applied to non-glaucomatous eyes. The excellent agreement of the in vivo and in vitro data for facility of outflow on the same eyes further justifies the assumptions and simplifications inherent in Grant's [9] formulation for tonographic estimates. It certainly adds security to the interpretations resulting from careful tonographic studies.

The perfusion method for measurement of intraocular pressure and facility of outflow is obviously of very limited clinical use per se. However, in addition to

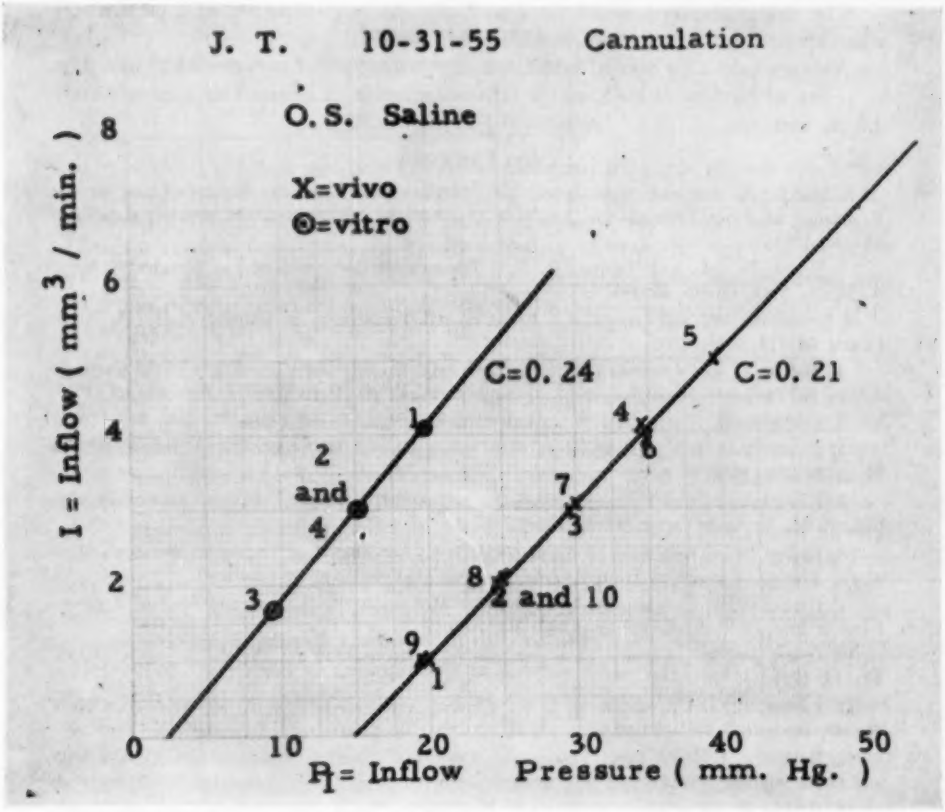

Fig. 5.—Perfusion data in vivo and in vitro of Patient J. T. (compare with lower tracing, Fig. 3).

establishing the validity of tonographic measurements, it is evident that this versatile method can be applied to animal eyes of many species because it is independent of such variable factors as size of the eye, scleral rigidity, and corneal curvature, which markedly influence tonography. Work is in progress applying such methods to guinea pigs and cats.

The finding of so little change (10%-15%) in facility of outflow following enucleation makes the extensive evaluation of factors contributing to this resistance to outflow in vitro of enormous clinical importance. The outstanding work of

Bárány || in modifying the outflow capacity by enzymes, surgical procedures, and metabolic inhibitors is provocative. Such basic work on enucleated eyes provides a most exciting stimulus and lays the groundwork for application to the living animal eye by in vivo perfusion. It is hoped that this type of approach will provide important advances in the understanding of the nature of the outflow mechanism and some of the factors contributing to its regulation.

SUMMARY

Facility of outflow has been measured by tonography and perfusion methods both in vivo and in vitro.

The values obtained by all three methods are in good agreement, particularly when applied to the same eyes of rabbits and patients.

Average values for normal rabbit eyes are an intraocular pressure of 19 mm. Hg, a facility of outflow of 0.35, and a rate of secretion of aqueous of approximately 3.5 cu. mm/min.

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Streptococcal Antihyaluronidase in Uveitis and Primary Glaucoma

Turbidimetric Measurement

JOSEPH W. HALLETT, M.D.
IRVING H. LEOPOLD, M.D.
and
SUSAN INWALD, Philadelphia

In an effort to obtain addittional evidence of the importance of prior or concurrent hemolytic streptococcal infection in the etiology of uveitis, Leopold and Dickinson [1] measured the antihyaluronidase and antistreptolysin titers in 63 cases of uveitis chosen at random from the ward service at the Wills Eye Hospital. They pointed out that in Woods' * classification of endogenous uveitis into granulomatous and nongranulomatous types the hemolytic Streptococcus has been suggested as the principal offender in the latter type.

Characteristically, the growing hemolytic Streptococcus secretes into the surrounding tissue a number of independently acting extracellular substances, among the most important of which are streptococcal hemolysin (or streptolysin) and streptococcal hyaluronidase.[4] Being protein in nature, these substances can act as antigens and produce specific antibodies in the blood stream.† These antibodies are present in at least low titer in the serum of most adults (for all mankind is more or less exposed to these common pathogenic bacteria).[7] Harris and Harris ‡ found the geometric mean titer for both antibodies to be raised slightly in convalescent scarlet fever and markedly in acute rheumatic fever. Using the normal values found by the latter authors § and the facilities of their laboratory, Leopold and Dickinson found, by statistical analysis of their results, suggestion that the hemolytic Streptococcus may play an etiologic role in the production of uveitis. They also felt that particularly the antihyaluronidase titer should be studied further as a possible method for detecting the etiology in cases of uveitis. In pursuit of that desideratum, the present study was undertaken. Meanwhile, Smith and Ashton [11] have reported a significant increase in antistreptolysin titers in anterior uveitis.

Dr. Paul Carmichael called our attention to the fact that di Ferdinando and Sega [12] found an increase in antihyaluronidase activity of the blood serum in 15 cases of chronic simple glaucoma. Obviously, this demands corroboration, and we have, accordingly, accepted in this study the additional task of evaluating the blood serum streptococcal antihyaluronidase levels in a group of patients with chronic simple glaucoma.

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From the Research Department, Wills Eye Hospital.

* References 2 and 3.
† References 5 and 6.
‡ References 8 and 9.
§ References 9 and 10.

METHODS AND MATERIALS

The three physicochemical methods now available for antihyaluronidase testing are the mucin-clot-prevention test, the turbidimetric test, and the viscosimetric test. The turbidimetric test is the most accurate [13] and was, therefore, the method chosen for this study.

The enzyme, streptococcal hyaluronidase, was prepared for us by Dr. George H. Warren, of the Wyeth Institute of Applied Biochemistry, Philadelphia, from a strain of Group A β-hemolytic Streptococcus, obtained through the courtesy of Dr. T. N. Harris, of the Children's Hospital, Philadelphia. The substrate, hyaluronic acid, was furnished us in the form of potassium hyaluronate by Dr. H. E. Alburn, also of the Wyeth Institute of Applied Biochemistry, who prepared it from bovine vitreous humor.

Standardization of Substrate and Enzyme.—The final indicator reaction of the turbidimetric test is the formation of a precipitate when the substrate is mixed with a 1 : 40 dilution of acidified horse serum. The turbidities are read in a Klett photoelectric colorimeter. We found 0.1 mg. of substrate per tube to be the optimal concentration that would produce turbidity readings within the most accurate range of the colorimeter. Keeping the substrate constant at 0.1 mg. per tube, titration with increasing amounts of enzyme produces a S-shaped curve. The curves of many such titrations cross at a point which corresponds to a Klett reading of 30. This most reproducible point was, therefore, chosen as the arbitrary end-point of the titration and was found to result from an average concentration of 0.055 mg. of enzyme. Three times this amount, or 0.165 mg. of enzyme per tube, was found to be very close to the end-point for most curves as they asymptotically approach the zero turbidity reading. Thus, by keeping the amount of enzyme constant at 0.165 mg. per tube, when in any titration for antihyaluronidase the arbitrary turbidity end-point of 30 is reached, two-thirds of the total amount of enzyme must be neutralized. This leaves one-third, or 0.055 mg., of enzyme intact. The latter amount, as we noted above, produces the arbitrary turbidity end-point of 30.

Procedure for Antihyaluronidase Titer.—A fasting specimen of 5 to 10 cc. of blood is collected with a dry syringe and needle and allowed to coagulate in a dry test tube. The clot is loosened with a sterile probe and the tube then centrifuged at 20,000 rpm for 15-20 minutes. The serum is inactivated in a 56-58 C water bath for 30 minutes in order to prevent interference by nonspecific inhibitors of hyaluronidase.[14] The inactivated serum is refrigerated without preservatives until used.

Klett tubes, 12 to 13 in number, previously scrupulously cleaned in Alconox, rinsed 10-20 times in distilled water, and then either air-dried or oven-dried (105 C), are set up in racks. Into each tube 0.4 cc. of 0.1 M acetate buffer solution, pH 6, is deposited with a Brewer automatic pipetting machine. An additional 0.3 cc. of the buffer solution is hand-pipetted into the first dilution tube (usually 1 : 8). Into the same first dilution tube 0.1 cc. of the serum to be tested is hand-pipetted, resulting in a total volume of 0.8 cc. From the first tube 0.4 cc. is pipetted out and placed in the second tube, producing a 1 : 16 dilution of serum there. The successive twofold dilutions are thus carried on down the line of tubes to 1 : 1024 or 1 : 2048. From the last tube 0.4 cc. is pipetted out and discarded.

At this point a row of γ-globulin control tubes are set up. In the first tube 0.75 cc. of buffer solution and 0.05 cc. of commercially available γ-globulin are deposited. All the rest of the tubes receive 0.4 cc. of buffer solution. From the first tube 0.4 cc. is pipetted into the second tube, leaving a 1 : 16 dilution in the first tube. Similarly, 0.4 cc. is pipetted from the second tube into the third, leaving a 1 : 32 dilution in the second tube. Twofold serial dilutions are thus successively produced down to a 1 : 4096 dilution. From this last tube 0.4 cc. is pipetted out and discarded.

In addition, as further serum controls, two rows of previously determined blood serums are set up in the same twofold dilutions as those described for γ-globulin. These blood serums are best changed often to insure that the work is not checked against deteriorating serums.

There are now four racks of Klett tubes, each marked with their dilution and containing 0.4 cc. of that serum dilution. Into each of these tubes, as a filler, 0.2 cc. of fresh isotonic salt solution is machine-pipetted. Into each tube there is now hand-pipetted 0.2 cc. of the enzyme solution containing 0.3 mg. of streptococcal hyaluronidase. This solution is prepared by dissolving 54 mg. of the enzyme in 36 cc. of 0.1 M acetate buffer solution, pH 6.0.

From this point on, each rack is handled separately. Fifteen minutes is allowed to elapse between the completed pipetting of the enzyme solution and the next step, which is the addition of the substrate. Into each tube 0.2 cc. of a solution containing 0.1 mg. of hyaluronic acid is

machine-pipetted. This solution is prepared by dissolving 50 mg. of hyaluronic acid and 1620 mg. of sodium chloride crystals in 100 cc. of 0.1 M acetate buffer solution, pH 6.0.

The racks are well shaken and placed in a 37.5 C water bath for 20 minutes to permit adequate antibody-enzyme-substrate reaction. Then, to terminate the reactions, the racks are placed in a 60 C water bath for five minutes. The racks are cooled by spraying the bottoms of the tubes with cold water and then by immersing the racks in an ice water bath for 5 to 10 minutes. Upon removal from the bath, each tube is dried with a linen dish towel.

To each tube is then machine-pipetted 4.0 cc. of an acidified horse serum solution. To prepare the latter, 56.8 cc. of glacial acetic acid, 1943.2 cc. of distilled water, and 590 cc. of 0.5 M solution of sodium acetate are mixed with sufficient concentrated hydrochloric acid to bring the pH down to 3.1-3.5; then one-fortieth by volume (approximately 65 cc.) of sterile horse serum without preservatives is added. The racks remain at room temperature for 30 minutes and are then read on the Klett-Summerson photoelectric colorimeter, using the blue filter.

At the same time that the serum control tubes are set up, a "zero" tube, a "high" tube, and a "low" tube are also prepared. The zero tube contains 0.8 cc. of buffer solution and 0.2 cc. of saline solution. The enzyme or substrate is added, but otherwise the tube is handled exactly the same as all the other tubes in the water bath, etc. Finally, 4.0 cc. of acidified horse serum is added to this tube. The high and low tubes are similarly handled. The high tube contains 0.6 cc. of buffer, 0.2 cc. of saline, and 0.2 cc. of substrate; later 4.0 cc. of acidified horse serum is added. The low tube contains 0.4 cc. of buffer, 0.2 cc. of saline, 0.2 cc. of enzyme, and 0.2 cc. of substrate; later 4.0 cc. of acidified horse serum is added.

The colorimeter is zeroed with the zero tube. Then the high and low tubes are read. Finally, each row of dilution tubes is read, starting with the γ-globulin, then the two rows of control serums, and then the unknown serums. Usually 10 minutes is allowed to elapse between the additions of the enzyme to each rack, so that each rack would stand at room temperature no longer than 30-40 minutes before being read. Several times during the readings the zero tube is again inserted into the colorimeter to check the accuracy of the machine.

TABLE 1.—*Age Range of Study Group*

Age, Yr. →	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	Total	Mean
Female	0	1	11	11	9	6	5	3	46	....
Male	2	6	6	11	12	3	4	0	44	....
Total	2	7	17	22	21	9	9	3	90	38.8

Determination of Titer.—It was found that commercial preparations of γ-globulin, pooled from approximately 2000 normal human blood serums, give repeatable titration curves. We arbitrarily chose a point on that curve approximately at the midpoint. This corresponded to a dilution of γ-globulin of 1 : 1830. Using the same Klett end-point, corresponding to 1 : 1830 for γ-globulin, we were able to obtain the titer for the unknown serum. For the sake of simplicity, these titers were, and hereinafter will be, recorded by the denominator of the titer fraction only; e. g., 1 : 1830 is equivalent to 1830.

Since the Klett readings usually fell somewhere between two consecutive twofold serial dilutions, further values between these dilutions had to be calculated. We interpolated 4 more titer units between each two consecutive twofold serial dilutions and recorded the Klett reading according to the nearest corresponding actual or calculated serial dilutions.

CLINICAL MATERIAL

A total of 90 patients with active uveitis were chosen at random from the wards and a few of the private services at the Wills Eye Hospital. There were 46 females and 44 males. Their ages ranged from 2 to 79 years, with a mean age of 38.8 years (Table 1). In this respect the group closely resembles that studied by Leopold and Dickinson.

It is relatively insignificant that the blood serums were usually obtained from each uveitis patient within the first few days of hospitalization, since the day of hospitalization bears no particular relationship to the onset of the uveitis. In 32 cases, after the patient's discharge from the hospital as cured or improved, we were able to obtain a second blood specimen for antihyaluronidase determination. The least number of days between collection of the first and second specimens was 12 days; the greatest number was 170 days, and the average number was 60.5 days.

All patients were routinely examined for foci of infection, syphilis, tuberculosis, Boeck's sarcoid, lymphogranuloma venereum, brucellosis, diabetes, and blood dyscrasias. Other miscellaneous factors were investigated where indicated. By application of Woods' || criteria, the entire group was found to consist of 49 cases of granulomatous and 41 cases of nongranulomatous varieties.

An additional effort to determine the relationship between concurrent or recurrent streptococcal infections and uveitis was made by filling out a questionnaire for each case. This covered such matters as the time of occurrence and type of treatment for rheumatic fever, pneumonia, streptococcal infection, sore throat, growing pains, upper respiratory infections, arthritis, and rheumatism.

The filling out of the questionnaire also aided us in setting up a normal control group. Forty healthy persons, including medical personnel and patients presenting themselves for such conditions as ametropia or ocular motility disturbances, who were free of uveitis and glaucoma and had had no, or no recent, affliction with the diseases listed in the questionnaire, were chosen for blood serum antihyaluronidase study. The ages of this group ranged from 4 to 81 years, with a mean age of 31.6 years (Table 2). In addition, through the courtesy of the Red Cross, we obtained blood specimens from 286 normal healthy blood donors. The ages of this group were between 18 and 65 years. No further information was at hand concerning age group or sex.

TABLE 2.—*Age Range of Control Group*

Age, Yr. →	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-90	Total	Mean
Female.....	0	1	6	4	2	0	0	2	1	16	....
Male.....	1	4	13	2	3	1	0	0	0	24	....
Total....	1	5	19	6	5	1	0	2	1	40	31.6

TABLE 3.—*Streptococcal Antihyaluronidase Titers*

Group	No.	Geometric Mean Titer				
Normal.....	326		97	(±7.5)		
Uveitis						
Total.....	90		84	(±8.6)		
Nongranulomatous.....	41		97	(±7.4)		
Granulomatous.....	49		73.5	(±9.5)		
Repeat uveitis						
Total.....	32	1st	97	(±8.8)	2d 64	(±8.6)
Nongranulomatous.....	12	1st	152.5	(±8.6)	2d 97	(±10.2)
Granulomatous.....	20	1st	73.5	(±8.3)	2d 48	(±6.9)
Glaucoma.....	40		73	(±7.4)		

For the glaucoma study, 40 patients, 20 men and 20 women, were chosen at random from the glaucoma clinics at the Wills Eye Hospital. They were all under active treatment for chronic simple glaucoma for various periods of time. The youngest was 26 years of age; the oldest, 89 years, and the mean age, 60.7 years.

RESULTS

The geometric mean titer was computed in all instances (Table 3) because the serum dilutions used in the test comprised a geometric series of decreasing concentrations. Statistical analysis yielded the standard deviations, which are expressed in serum dilution steps based upon four interpolated steps between each two consecutive twofold serial dilutions.

The geometric mean titer of 286 normal Red Cross bloods was 97, with a standard deviation of ±7.5. The geometric mean titer of the 40 normal persons was 73.5, with a standard deviation of ±9.9. The values for the total of 326 normal bloods were the same as those for the Red Cross group.

|| References 2 and 3.

The geometric mean titer of the 90 patients with uveitis was 84, with a standard deviation of ±8.6. The 41 cases of nongranulomatous uveitis had a geometric mean titer of 97, with a standard deviation of ±7.4. The 49 cases of granulomatous uveitis had a geometric mean titer of 73.5, with a standard deviation of ±9.5.

In the 32 cases of uveitis in which a second antihyaluronidase titer was obtained, the geometric mean titer for the first specimen was 97 and the standard deviation ±8.8, and that for the second specimen was 64 and the standard deviation ±8.6. This group, of 32 cases, was made up of 12 cases of nongranulomatous and 20 cases of granulomatous uveitis. The geometric mean titer for the first specimen in the nongranulomatous group was 152 (±8.6) and for the second specimen 97 (±10.2). In the granulomatous group the titer changed from 73.5 (±8.3), in the first specimen, to 48 (±6.9), in the second.

In the 40 cases of chronic simple glaucoma a geometric mean titer of 73 (±7.4) was obtained.

COMMENT

Comparison of the geometric mean titer of 84 for the entire uveitis group with the expected titer of 97 for the normal population in this vicinity reveals a total lack of significance for the antihyaluronidase levels in uveitis. It is true that the nongranulomatous varieties present a higher mean titer (97) than the granulomatous varieties (73), but the figure is still not higher than that for the normal population. This is in distinct contrast to the findings of Leopold and Dickinson. Apparently, the basic reason for the discrepancy is their lower normal values (between 24 and 36), as compared with the much higher normal value of 97 as we found it. It must be remembered that their normals were measured by the mucin-clot-prevention reaction, which produces titers approximately one-half lower than those resulting from the turbidimetric test.[14] It is also significant that their normal subjects ranged from the age of 6 months to young adulthood,[10] whereas our normals constituted an older, more adult, group and one which more closely approximated in age distribution our, as well as their, study group.

The significant fall in titer in the second specimens suggests that more importance should be placed upon the fluctuation of the titer during different stages of uveitis, rather than upon a single antihyaluronidase determination. This is in accord with many other similar phenomena in immunology; e. g., the complement fixation test in herpes simplex infections is more significant in its fluctuations than in its value relative to that of a normal group.[15]

Analysis of the questionnaires showed that 39 cases had, or were actively suffering from, a probable streptococcal infection. These 39 cases could be further subdivided into 23 (constituting 47%), of the nongranulomatous uveitis group, and 16 (constituting 39%), of the granulomatous group. This disparity in favor of the nongranulomatous group would tend to incriminate the streptococci in the etiology of that group. It must be noted, however, that such data, derived from the amanuensis, tend to be inaccurate. Furthermore, in many instances the relationship between the diseases listed in the questionnaire and streptococcal infection is conjectural.

It is important to realize that a diagnostic test, such as the antihyaluronidase titer, is limited by the overlapping of the frequency distribution of titers in the study and in the control group. It is the relative range of titers, rather than the relative mean titer, that is important. The comparison of range of titers involves the calculation of that titer having the same percentage of normal serums below it

as the percentage of uveitis serums above it. That percentage figure is called the IRD (index range difference). The higher the index, the greater the separation of the distributions of titers between the normal and the uveitis groups and the greater the usefulness of the test. An index of 50 indicates a worthless test, for then half the uveitis serums would have titers above the titer corresponding to the index and half the normals would have titers below it. A theoretical index of 100 would be ideal, for then the given test would be infallible in the laboratory diagnosis of the disease.

In Table 4 are listed the frequency distributions of antihyaluronidase titers in the normal and the uveitis cases. Calculation of the IRD, as described by Leopold and Dickinson, shows that for uveitis in general, and granulomatous uveitis in particular, this test is without value. In nongranulomatous uveitis, on the other hand, it is of slight, but definite, value.

The geometric mean titer of the glaucoma patients is lower than that of the normal population. Reference to Table 4 indicates a low IRD. It is, then, obvious that chronic simple glaucoma is not associated with abnormally high streptococcal antihyaluronidase levels in the blood serum.

TABLE 4.—*Percentage Frequency Distributions of Antihyaluronidase Titers in Normal Subjects and in Patients with Uveitis and Chronic Simple Glaucoma*

		Uveitis			
Titer	Normal	Total	Granulomatous	Nongranulomatous	Glaucoma
8-8	3.1	5.5	10.2	0	2.3
10-16	3.7	5.6	6.1	4.9	0
18-32	11.7	16.7	14.3	19.5	30.8
36-64	19.6	13.3	12.2	14.6	12.9
74-128	27.5	20.0	22.5	17.1	28.2
150-256	17.5	25.6	20.4	31.7	12.9
304-512	11.0	6.7	8.2	4.9	12.9
600-1024	4.9	5.5	6.1	4.9	0
1180 up	1.0	1.1	0	2.4	0
		IRD=49.6 Titer=90	IRD=48.0 Titer=90	IRD=52.2 Titer=90	IRD=46.1 Titer=90

CONCLUSIONS

The blood serum levels of streptococcal antihyaluronidase were measured by the turbidimetric method in 326 normal persons, 97 patients with uveitis, and 40 patients with chronic simple glaucoma.

No increase in the geometric mean titer over that of the normal controls was found in any group.

The IRD indicated very slight value of the test in nongranulomatous uveitis, but not in any other group.

Fluctuations in the titer may be of more significance in uveitis than a single test for comparison with the normal population.

Until an easier and more rapid method for the turbidimetric measurement of antihyaluronidase is devised, we are convinced that the present method will have value only as a research procedure, and not as a routine clinical laboratory test.

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Cast-like Fungus Obstruction of the Nasolacrimal Duct

Report of a Case

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Yeast-like fungi as the cause of obstruction of the nasolacrimal duct are exceptional (Duke-Elder [1]). Numerous reports may be found, however, of various other fungi producing obstruction of the nasolacrimal passages.

Two unilateral cases of Candida albicans producing obstruction of the nasolacrimal duct were recorded by Fine and Waring.[2] Both cases were seen in women who complained of epiphora. Finally, after repeated unsuccessful irrigations, both women were spontaneously relieved by blowing from the nose a grayish-white, cylindric cast. In the first case this cast was 16 mm. long and 3 mm. in diameter, while in the second case it measured 10 by 2 mm. In both cases the cast was composed almost entirely of budding, yeast-like cells, which on histologic examination and culture proved to be C. albicans. In both cases there was immediate recovery following the extrusion of the cast-like obstruction of the duct without further treatment. The authors concluded, in both cases, that C. albicans was the cause of the formation of the cast in the nasolacrimal duct.

The reports of Fine and Waring are apparently the first, and only ones, of this rare but definite morbid entity to be described in the literature. It is our belief that the present case is the third occurrence of this disease to appear in the literature.

REPORT OF CASE

A 23-year-old white woman was first seen in the outpatient clinic of the ophthalmological department of the University of Michigan Hospital on Oct. 14, 1955. She presented a history of epiphora O. D. of two weeks' duration. This epiphora developed unceremoniously one morning and was persistent thereafter. The patient denied injuries in or about the face, as well as eye, upper respiratory, or sinus infections. She was in the second trimester of pregnancy.

The ophthalmological examination was entirely negative with the exception of an obvious epiphora O. D. with an associated hyperemia of the conjunctiva. Irrigation of the right nasolacrimal passageways was attempted. There was at first regurgitation of a small amount of white, curdy material from the upper punctum. An effort to probe the duct met with unyielding resistance and severe pain at 38 mm. Further attempts at irrigation and probing were made, without success, until finally a small amount of fluid was irrigated through into the nasal cavity.

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From the Laboratory of Neuropathology and Neuro-Ophthalmology, the Department of Ophthalmology, and the Department of Dermatology of the University of Michigan.

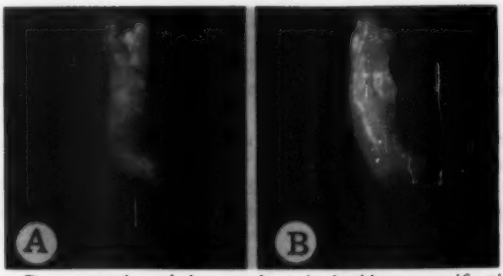
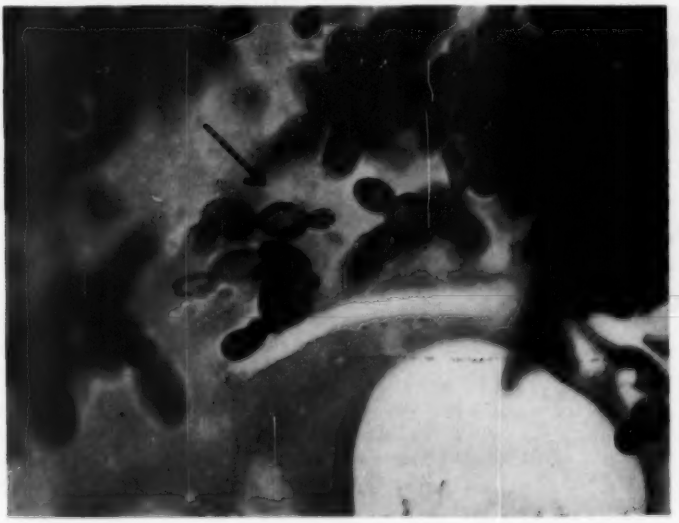


Fig. 1.—Demonstration of the cast from both sides; magnification × 3.

Fig. 2.—Thin-walled septate hyphae fragments within the exudate of the cast. Periodic-acid-Schiff stain; reduced to 76% of mag. × 400.

Fig. 3.—Blastospore formation within the exudate of the cast. Periodic-acid-Schiff stain; reduced to 76% of mag. × 200.

Fig. 4.—High-power view of thin-walled, single-budding, yeast-like cells (Candida albicans). Periodic-acid-Schiff stain; reduced to 88% of mag. × 1000.



The patient was given a solution of 30% sulfacetamide (Sulamyd) sodium to instill in the right eye four times a day and was instructed to follow the drops with a massage of the nasolacrimal duct.

Two weeks later the patient returned to the clinic stating that she had experienced a recurrence of epiphora shortly after her clinic visit. This had persisted until the preceding day, when, after the use of the drops (sulfacetamide, 30%) and massage, she noted the sensation of fluid passing down into her nose. She then blew her nose and recovered a small cast (Fig. 1), which was followed by a small amount of blood. Immediately thereafter she was relieved of her epiphora.

Pathologic Description of Cast.—The patient, intelligently, put the cast into alcohol for fixation. This made it possible to study the cast histologically but, unfortunately, prevented cultural examination.

The cast was 9 mm. long and 2.5 mm. in diameter. Its color was yellowish-white (possibly an effect of the alcohol fixation). Figure 1 demonstrates the cast from both sides. The cast, after imbedding in paraffin, was cut in serial sections on the microtome. Several sections were stained with hematoxylin and eosin, and the remainder with the periodic-acid-Schiff stain for detection of fungi.

The greater proportion of the cast was comprised of exudate, which contained a few round cells, leucocytes, and remnants of nucleated epithelial cells. There was no foreign body or other structure within the cast which could be considered to have been a nucleus for the deposition of the dense exudate.

The periodic-acid-Schiff technique revealed the presence of numerous thin-walled septate hyphae fragments throughout the entire cast (Fig. 2). In addition to the hyphae, there were areas in which the fungus showed blastospore formation (Fig. 3). These were collections of numerous thin-walled, oval, single-budding, yeast-like cells which were approximately 2μ-4μ in size (Fig. 4). The appearance of these structures throughout the cast was most comparable to the growth pattern of a member of the genus Candida and undoubtedly represented C. albicans. It was impossible, unfortunately, to prove the positive identity of the causative fungus by culture, since the cast had been preserved in alcohol.

SUMMARY

A case of unilateral epiphora due to obstruction of the nasolacrimal duct by a cast-like formation is described. Histologically, fungi were demonstrated and C. albicans was considered as being the most likely etiological agent.

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An Initial Evaluation of Prednisone Therapy in Ocular Inflammation

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Recent clinical trials of prednisone therapy in active rheumatoid disease have revealed a potency several times as high as that of cortisone and its analogues.* Of added significance is the absence of a corresponding increase of side-effects, indicating that this drug may apparently be more suitable for long-term steroid therapy.

This report concerns an initial evaluation of prednisone in the treatment of ocular inflammation. For this purpose, the investigation was carried out in two parts: an examination of the response in experimental uveitis and a second, clinical study.

EXPERIMENTAL UVEITIS STUDIES

Evaluation of the anti-inflammatory action of prednisone was based on the results of three series of animal experiments: The initial two were carried out by collating the drug with cortisone, hydrocortisone, and corticotropin (ACTH), while the third served to examine prednisone potency alone. Significant features of the series were as follows:

Series I. Comparative blocking effects of steroids and corticotropin administered prior to induction of activity in experimental uveitis

Series II. Comparative anti-inflammatory effects of steroid and corticotropin given subsequent to the onset of uveitis

Series III. Estimate of prednisone potency in the treatment of active experimental uveitis studied by serial reduction of dose

Experimental uveitis was induced by the intravitreal injection of 0.1 cc. of undiluted horse serum (Lilly) into animals sensitized to this antigen by previous subcutaneous injections. On the basis of slit-lamp observation, four features of the resulting lesion were chosen for grading. These were (1) aqueous flare, (2) aqueous cellularity, (3) fibrinous exudate content of the anterior chamber, and (4) vascularity of the albino iris. Slit-lamp examinations of all eyes were made every 48 hours.

Studies of the blocking function of prednisone and of its immediate anti-inflammatory effects on established uveitis require experimental lesions of differing severity. Essentially, this is because the full response of a nonmoderated lesion tends to obscure the effects of prophylactic therapy. In the case of horse serum uveitis, the necessary moderation of response was obtained by reducing the time between the sensitizing injection and the intravitreal shock dose injection, plus a change in

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* References 1 and 2.

sensitizing technique, to be described later. Consequently, the method of Vogel [3] was employed to induce a uveitis of moderate severity (Series I), while the actual treatment of established lesions (Series II and III) utilized the maximal activity following use of the Schlaegel and Davis technique.[4] Profiles and features of the two types of lesions resulting from an application of these techniques are shown in Figures 1 and 2.

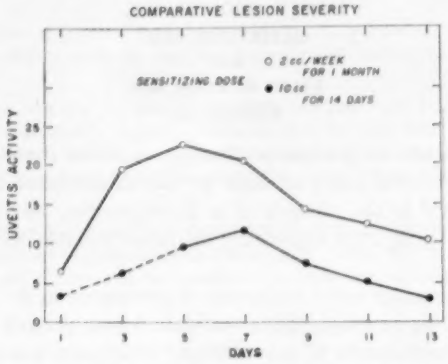

Fig. 1.—Definite increase of uveitis activity was noted when the Schlagel and Davis technique was employed. Each recorded value presents total (+) activity of 10 eyes.

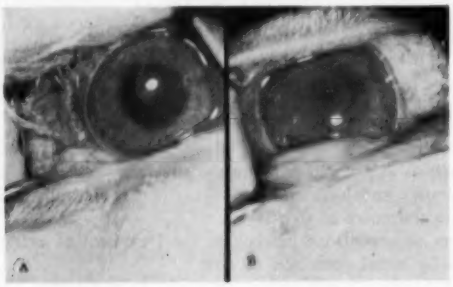

Fig. 2.—*A*, typical moderated uveitis response at the 48-hour interval obtained by the use of techniques of Vogel; i. e., a subcutaneous injection of 10 cc. of horse serum was given 14 days prior to the intravitreal injection of 0.1 cc. of the same serum in rabbit eyes.

B (Series II and III), near-maximal response in rabbit eyes observed at the 48-hour interval when the technique of Schlagel and Davis was employed. This method involved the use of four injections (subcutaneous) of 0.5 cc. of horse serum (four sites), which were repeated weekly for 21 days to give maximal cutaneous sensitivity. An intravitreal injection of 0.1 cc. was then given on the 28th day.

Series I: Comparative Blocking Effect of Steroids and Corticotropin

The inflammatory blocking effects of prophylactic therapy were studied by limiting treatment to a 48-hour period prior to the induction of ocular lesions.

Technique.—Twenty-five adult albino rabbits (1750 to 2300 gm.) received 10 cc. injections of undiluted horse serum beneath the shaved abdominal skin. Twelve days later the animals were divided into five groups of five each and treatment consisting of intramuscular injections was begun, according to the following scheme:

Group 1	Cortisone acetate	25 mg/kg.
Group 2	Hydrocortisone acetate	25 mg/kg.
Group 3	Prednisone alcohol	5 mg/kg.
Group 4	Corticotropin (Armour)	10 units/kg.
Group 5	Saline (control)	2 cc. I. M.

These injections were repeated in 24 hours, i. e., on the 13th day. One day following this, intravitreal injections of serum were given through the pars plana region of each eye, using a 26-gauge needle and a tuberculin type syringe. The amount of serum injected into each eye was 0.1 cc., and sterile technique was observed. These shock dose injections were given on the 14th day, i. e., 24 hours following the last intramuscular steroid injection. The four features previously mentioned were subsequently graded by slit-lamp examination every 48 hours. Conjunctival chemosis and vitreous opacities were not so graded because of their proximal relationship to the injections.

Results.—Dosage levels chosen for cortisone hydrocortisone and corticotropin were guided by the highest milligram/kilogram levels employed in previous experimental studies of steroid therapy (Table 1). As a test of its potency the prednisone dosage was held to a level one-fifth that of the other steroids.

TABLE 1.—*Dosage Schedule Followed in Series I and II* *

Group	Treatment	Daily I. M. Dose	Human 70 Kg. Equivalent
1	Cortisone	25 mg./kg.	1750 mg.
2	Hydrocortisone	25 mg./kg.	1750 mg.
3	Prednisone	5 mg./kg.	350 mg.
4	Corticotropin	10 units/kg.	700 units
5	Saline	1 cc./kg.	70 cc.

* The cortisone and hydrocortisone dosage of 25 mg. per kilogram, as used in previous studies,[6] is seen to represent a high human equivalent dosage. Prednisone, by contrast, was administered in one-fifth the dose of the other steroids, i. e., 5 mg. per kilogram. The corticotropin level was suggested by those used in previous published reports.[5]

As noted in preliminary studies, activity in the control eye reached its peak on the seventh day, and it was at this juncture that the greatest difference between control and treated eyes was observed. Although the activity in all treated eyes was definitely moderated, in contrast to the pattern of the control group, there was no single instance in which therapy completely blocked the onset of the lesion activity. The most complete blocking effects were recorded in two of the five prednisone-treated animals. Over-all, the suppressive influence of prednisone, given in one-fifth the dose, was equal to that of cortisone and hydrocortisone (Fig. 3).

Animals given the prophylactic corticotropin injection showed less response during the first seven days of lesion activity, indicating a definite latency in the performance of this drug in experimental uveitis. In general, beyond the

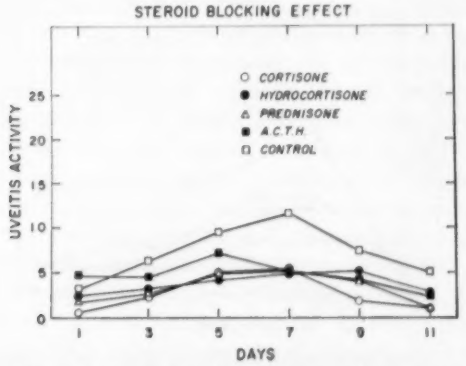

Fig. 3 (Series I).—When only prophylactic therapy was given, the greatest difference between control and treated eyes appeared on the seventh day. This effect was noted in nearly equal degree in all treated animals. Each recorded value represents the total (+) activity of 10 eyes.

seventh day, the lesion, as seen in all groups of treated animals, tended to follow, at a lower level, the regressive course of the control group. It appears, therefore, that such prophylactic therapy, while suppressing the initial activity of the lesion, does not significantly shorten the period of resolution which follows the attainment of maximal activity. The duration of lesion activity in most instances, treated and control alike, was from 13 to 15 days. No reactivation of the lesion was noted beyond this time.

Series II: Treatment of Established Lesions

The effect of prednisone on 24-hour-old lesions was studied by withholding treatment for that period of time beyond the moment of intravitreal serum injection. To bring about a severer type of inflammation, an increase of the time interval to 28 days between the sensitizing and the shock dose was combined with the production of a high degree of cutaneous sensitivity.

Technique.—The method described by Schlaegel and Davis was used in this series.[4] Twenty-five adult albino rabbits (1700 to 2400 gm.) were given weekly subcutaneous injections of the serum over a 21-day period. Each weekly sensitizing dose consisted of four separate 0.5 cc. injections given beneath four discrete abdominal skin areas. Arthus type necrosis of the abdominal skin was commonly observed within 15 days and was invariably present beyond the 21st day. This sign was taken as an indication of maximal cutaneous sensitivity. Seven days following the third, and final, subcutaneous injection, i. e., 28 days after the initial one, the intravitreal shock dose injection of 0.1 cc. was given. The resulting lesions were of more rapid onset (12-24 hours), and all of the four graded features were of much more prominent intensity than those observed in Series I (Figs. 1 and 2).

Dosage schedules were again calculated to give prednisone in one-fifth the levels of cortisone and hydrocortisone. Treatment began 24 hours after lesion induction and was repeated daily for one week. Slit-lamp observations were recorded every 48 hours, as in previous studies.

Results.—Control eyes in this series, as graded by their inflammatory signs, showed evidence of maximal inflammation on the 5th day and revealed the most rapid progress during the first 72 hours of activity. By contrast, all steroid-treated eyes displayed a greatly reduced activity during the first 72-hour period. Figure 4 shows how definite was this effect in the prednisone-treated group as compared with the cortisone and hydrocortisone groups. The four signs of uveitis taken separately or as a combined graded value, were much less severe in the prednisone

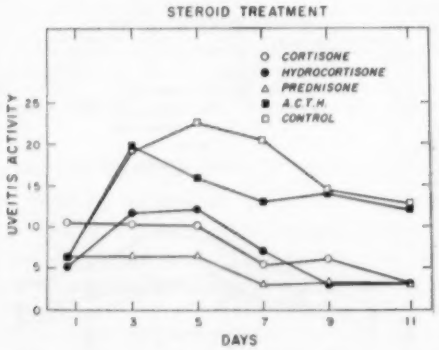

Fig. 4 (Series II).—When treatment of established uveitis was continued for one week, all groups receiving steroids showed the greatest deviation from the control animal pattern during the five- to seven-day interval. In this series, treatment was withheld for 24 hours following onset of uveitis activity. The enhanced effect of prednisone in comparison with other steroids, plus the latency of the corticotropin effect, are demonstrated.

group than those noted in any or all of the other groups. While the seven-day treatment course with prednisone gave a more rapid initial suppression of activity, a low, but nonextinction, level of inflammation was sustained, nearly equal to that found with the other steroids. Beyond the ninth day, however, three steroid-treated groups revealed a significant and nearly equal decline of activity. The greatest suppression of lesion activity by such treatment appeared in the seven- to the nine-day interval.

Corticotropin treatment of this lesion tended to give a response pattern separate from that of the steroid groups, indicating, again, the latency of its effect. Indeed, had not its performance on rabbit uveitis been demonstrated previously,[5] so closely did it follow the control group in the 1- to 3-day, and 9- to 12-day intervals, one would almost doubt the efficacy of corticotropin in this particular group of animals. In this acute animal lesion at least the superiority of steroid therapy in general, and of prednisone in particular, over bovine corticotropin (Armour) was definite. When observations were extended beyond the 12-day interval, shown in Figure 4, there was no rebound or recurrence of activity up to the 17th day.

Series III: Quantitation of Prednisone Effect on Established Uveitis

Technique.—The procedures detailed for induction of lesions in Series II were repeated on 15 adult albino rabbits (1825 to 2300 gm.). Five groups of three animals each comprised this series, and daily treatment was given according to the following schedule:

Group 1: 5 mg. prednisone per kilogram
Group 2: 3 mg. prednisone per kilogram
Group 3: 1 mg. prednisone per kilogram
Group 4: 0.5 mg. prednisone per kilogram
Group 5: 2 cc. isotonic saline

All injections were intramuscular, and, as before, slit-lamp examination was carried out every 48 hours.

Results.—All treated animals underwent a much greater suppression of activity in their uveitis than did the controls. Among the four groups receiving prednisone, in a dosage ranging from 0.5 to 5.0 mg. per kilogram, only minor differences in the degree of lesion response were noted during the seven days of treatment. Furthermore, these differences in response were gradually resolved, with the result that all treated groups showed a nearly equal total activity value on the 8th day, 24 hours after therapy was discontinued. This coincidence is of doubtful reproducibility and is, no doubt, the result of interpretive errors inherent in our grading system. Nonetheless, the nearly maximal suppression in all 12 treated eyes, noted on this eighth day, seems to point to a significant trend, when time intervals are considered in relation to therapeutic effects. A similar pattern of maximal response, during the seven- to the nine-day interval, was noted in all 15 eyes treated with cortisone, hydrocortisone, and prednisone in Series II. It is probable that in this type of lesion, therefore, a necessary interval of seven to nine days must obtain before clearing of inflammatory signs becomes maximal, irrespective of the dosage or the nature of the steroid employed. As interpreted here, this interval represents the time required for completion of two processes: suppression of current inflammation and the subsequent or simultaneous removal of accumulated products. Since each process may contribute to the picture of uveitis activity, a need for sustained steroid therapy is implied. Suppression of activity depends on a continuity of adequate steroid levels, for, as shown in Figure 5, the reactivation, which occurred when medication stopped, was limited to those animals receiving less than 1 mg.

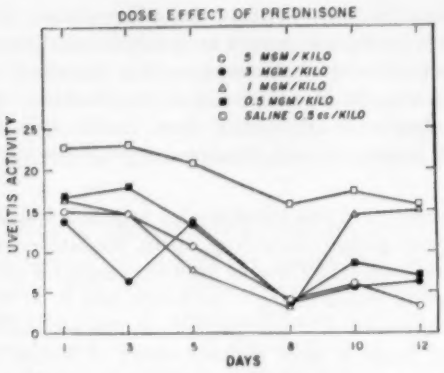

Fig. 5 (Series III).—This graph shows the near-equal suppression of uveitis by the eighth day, irrespective of prednisone dosage given for seven days immediately preceding this time. A recurrence of activity was noted when animals receiving less than 1 mg. per kilogram had treatment discontinued.

of prednisone per kilogram of body weight. No such rebound was noted in animals receiving 3 or 5 mg. per kilogram, even when the observation period was extended to 17 days. Thus, the necessity of adequate maintenance dosage becomes evident. In a similar report dealing with cortisone potency,[5] Woods reported a significant difference in the response of experimental uveitis to cortisone over a range of 2.5 to 10 mg. per kilogram, despite the use of both prophylactic and active treatment injections. With prednisone no difference is observed here over a range of 1.0 to 5.0 mg. per kilogram, despite the fact that treatment was withheld until the lesions were 24 hours old.

CLINICAL STUDIES

Patients included in this report represent problem cases referred to the National Institutes of Health because of poor initial response to routine steroid therapy, or because of uncontrolled recurrence of uveitis. As such, they do not resemble a typical sampling of clinic populations. What follows, therefore, is in the nature of a preliminary report, from which only cautious judgments may be derived. According to the pathology of the lesions, the patients in this series may be divided as follows:

Group I. Iridocyclitis (Table 2)
- A. Acute.....6 cases
- B. Chronic.....5 cases

Group II. Miscellaneous Conditions (Table 3)
- A. Episcleritis.....1 case
- B. Optic neuritis.....3 cases
- C. Granulomatous posterior uveitis.....3 cases
- D. Amyloid disease.....1 case
- E. Allergic conjunctivitis.....1 case

Treatment by local instillation of the prednisone suspension was employed in seven patients in this series—six with iridocyclitis and one with conjunctivitis. The preparation used was a 0.5% suspension of prednisone alcohol in a 1% methylcellulose and saline solution. This dose was given every two hours during the acute phase of inflammation and was reduced as improvement was evident.

The general scheme for oral systemic therapy consisted in the administration of 40 mg. of prednisone the first day, followed by 30 mg. on the second day, and by 20 mg. daily through

the period of active inflammation. Further adjustment of dosage was made on an individual basis, the daily dose being increased to 40 mg. for reactivation of lesions and reduced to 10 mg. for follow-up care of chronic conditions.

GROUP 1: *Iridocyclitis.*—It is from this group of 11 patients, each with a form of iridocyclitis, that the most significant conclusions are drawn.

Six acute episodes of iridocyclitis were treated, three with local and three with systemic prednisone. The general subjective response was gratifying in that all patients experienced definite relief within 24 hours and were symptom-free by the 7th day of treatment. Complete clearing of the anterior segments required three weeks, however, and in two patients with acute disease overlying a chronic base a continuous low-grade activity remained evident despite therapy (Cases 4 and 10, Table 2).

It appears that the time required to effect a response under prednisone therapy is about equal to that observed in a type of iritis responsive to cortisone or hydrocortisone.

Among these six acute cases, four reported a previously unsatisfactory response to cortisone therapy. These verbal reports, and those of patients in similar circumstances, cannot be recorded as definitely refractive to cortisone-hydrocortisone therapy, however, until the effects of increased dosage, or of combined local and systemic dosage, with these steroids have been studied. Neither is it possible always to verify a patient's reliability or the actual periodicity of steroid administration prescribed elsewhere. In forming an indictment of previous cortisone-hydrocortisone therapy, therefore, the conservative approach appears best in this group.

The significance of prednisone performance lies in the fact that, when given in low dosage, it brings about a cortisone-like suppression of acute iridocyclitis. Further, it is able to effect this response in certain cases that did not benefit from a previous trial of such cortisone-hydrocortisone therapy.

Chronic iridocyclitis was treated in five patients, three by systemic means and two locally. All five had previously recorded a poor response to cortisone-hydrocortisone therapy. In three cases the condition was of sarcoid etiology, and in one it was heterochromic cyclitis. A fifth, chronic, case was a rheumatoid etiology. All five showed low-grade activity of long duration without recent acute flare-up. The response in this group was not impressive, and when prednisone therapy failed to exceed the results of previous ineffective treatment after three weeks the treatment was abandoned.

GROUP 2: *Optic Neuritis.*—Systemic prednisone therapy was used in three cases of optic neuritis, with satisfactory results in two of them.

A patient whose response to cortisone therapy had been poor showed improvement of visual acuity from 20/400 to 20/50 following 24 days of prednisone therapy (Case 7, Table 3). A second patient received adequate maintenance therapy with 10 mg. of prednisone daily, instituted after his initial acute episode had responded satisfactorily to intravenous and intramuscular corticotropin.

A most interesting sequence of responses appeared in a 27-year-old white women (Case 5), whose chronic, recurrent bilateral neuritis was of 18 months' duration. Initial blurring of vision attended the withdrawals of corticotropin and hydrocortisone therapy after a six-month period. Daily intake of 20 mg. of prednisone effected an initial improvement, but this was not sustained. When increased loss of vision followed in 48 hours, prednisone was discontinued. This condition then responded

TABLE 2.—*Data on Eleven Patients with Iridocyclitis Treated with Prednisone*

Case	Sex	Age	Diagnosis	Duration Present Episode	Treatment	Days to Symptom Relief	No. Days to Clearing of Inflammation	Previous Prescription	Comment
1	M	63	Acute iridocyclitis	2 days	Local prednisone (Meticortin) susp., 0.5%; mydriatics	5	30	None	Good result
2	M	33	Acute iridocyclitis	4 days	Local prednisone; mydriatics	1-7	25	Local cortisone and mydriatics	Good result
3	M	60	Acute iridocyclitis	3 wk.	Local prednisone; mydriatics	2-5	19-24	Phenylephrine; salicylates	Good result; recurrence 1 mo. later, with good response in 1 wk.
4	M	25	Acute iridocyclitis	24 hr.	Systemic prednisone (40, 30, 20 mg.); mydriatics	1	Continues low-grade activity (4 wk.)	Cortisone ointment; mydriatics	Good result; asymptomatic, although low-grade activity persists
5	F	47	Chronic iridocyclitis, rheumatoid	1 yr.	Local prednisone; mydriatics	.....	.....	Hydrocortisone, 2½% suspension	No improvement over hydrocortisone effect; continued low-grade activity
6	M	35	Chronic iridocyclitis	5 yr.	Local and systemic prednisone; mydriatics	Asymptomatic	.....	All possible treatment	Partial control, but no complete clearing
7	F	38	Chronic iritis, sarcoid	3 yr.	Local prednisone; mydriatics	.....	.....	Hydrocortisone 2½%	No improvement over hydrocortisone level
8	F	11	Chronic iritis, sarcoid	2 yr.	Systemic prednisone	.....	.....	Systemic cortisone	No improvement
9	F	39	Chronic iritis, heterochromia	1 yr.	Systemic prednisone	.....	.....	.....	No improvement
10	F	34	Acute iritis O. U. (recurrent)	2 yr.	Systemic prednisone	2-5	Cont. low-grade activity OD, OS, 14 days	Corticotropin; cortisone; hydrocortone; mydriatics	Good result
11	M	53	Acute iritis	5 wk.	Systemic prednisone; mydriatics	1-7	22	Cortisone; mydriatics	Good result

TABLE 3.—*Data on Prednisone Therapy in Various Ocular Diseases*

Case	Sex	Age	Diagnosis	Duration Present Episode	Treatment	Days to Improvement	Previous Treatment	Comment
1	F	64	Episcleritis, rheumatoid	4 mo.	Systemic prednisone	1	Local cortisone	Fair control for 5 mo.; relapse while on therapy
2	F	59	Granulomatous uveitis, toxoplasmic	7-8 mo.	Systemic prednisone; local prednisone; pyrimethamine and sulfonamides	7	Systemic cortisone	Good result with combined therapy
3	M	34	Granulomatous uveitis, toxoplasmic	? yr.	Systemic prednisone; pyrimethamine and sulfonamides	..	.....	Good result with combined therapy
4	F	65	Granulomatous uveitis, tuberculosis	18 mo.	Systemic prednisone	..	Antibiotics	Good improvement of vision and decrease in inflammatory signs
5	F	28	Chronic bilat. optic neuritis	18 mo.	Systemic prednisone	..	Corticotropin; hydrocortisone	No improvement; good results with subsequent corticotropin
6	F	43	Optic neuroretinitis	6 mo.	Systemic prednisone	..	Corticotropin	Continued improvement when used subsequent to corticotropin
7	F	34	Optic neuritis (recurrent)	2 yr.	Systemic prednisone	7	Cortisone	Good response; vision 20/400; 20/50 in 2½ wk.
8	M	..	Amyloid disease	12+ mo.	Systemic prednisalone	..	.....	No response
9	F	44	Allergic conjunctivitis	6 mo.	Local prednisone	..	Hydrocortisone	No response

dramatically to a renewal of intravenous corticotropin therapy. If one concedes that the prednisone dosage here was adequate, an assumption which is not at all proved, the possibility that all forms of the same lesion type do not respond to the same steroid must be given further consideration.

Posterior Uveitis, Granulomatous.—Systemic prednisone was combined with pyrimethamine and sulfonamide therapy in the treatment of two patients with toxoplasmic uveitis. In both instances it was felt that the time of posterior-segment clearing antedated, by several days, the expected time of clearing with chemotherapy alone. In accord with accepted principles of steroid treatment, prednisone was not administered in these cases until an initial response to chemotherapy was evident. For this reason, no claim for primary steroid effect can be made here with certainty.

A third patient, with nonspecific posterior granulomatous uveitis, likewise exhibited a rapid satisfactory clearing of the posterior segment under prednisone medication. No local prednisone therapy has been given in any posterior-segment disease in this series.

Episcleritis.—A patient with rheumatoid arthritis and episcleritis displayed marked symptomatic relief and objective improvement within 48 hours of the onset of prednisone intake. After five months of daily 30 mg. intake, however, an increase of symptoms and of inflammation of both eyes was evident. The possibility that a tolerance or a basic tissue resistance has developed merits further consideration.

Amyloid Disease.—Systemic amyloid disease, confirmed on biopsy in a 32-year-old white man, was accompanied by heavy vitreous opacity and faintly visible posterior fundus lesions. High doses of systemic prednisone effected no change in the status of this ocular condition, either during or after cessation of therapy.

Allergic Conjunctivitis.—One case of advanced follicular conjunctivitis, refractory to cortisone and hydrocortisone therapy, gave no response to local prednisone treatment. In some patients daily intake of oral prednisone for over three months has yet given no evidence of significant side-effects.

COMMENT

While the response of acute uveitis in animals to prednisone therapy has been wholly favorable, only certain of these results find application to the clinical problems at hand. Studies of the anti-inflammatory effect, in both the prophylactic and the active treatment of animal uveitis, indicate a potency about equal to that of other steroids given in doses five times as great. In general, this reputation was sustained in those *acute* human lesions which responded to it. An intake of 20 to 40 mg. per day appeared adequate for treatment of those acute ocular lesions which did respond. Certain of these results are at variance with the published reports of King and associates.[7] It is felt, however, that insufficient data are available here to permit a valid comparison of clinical studies.

The response of chronic anterior uveitis was not so impressive, however, in lesions previously uninfluenced by cortisone-hydrocortisone therapy. On the other hand, a group of patients with acute iritis is cited with good prednisone response, following poor results reported on initial cortisone or hydrocortisone medication. It is our feeling, however, that the adequacy of previous steroid or hormonal treatment is often suspect, and is influenced by several factors remote to the properties of the drugs themselves. Especially in the initial evaluation of prednisone therapy, results tending to deprecate the efficacy of previous steroid treatment should be applied with caution, pending a scrutiny of dosage and routes employed.

The time required for onset of anti-inflammatory effects, and for the total clearing of inflammation, is not materially reduced by the use of prednisone therapy, as compared with the results obtained with other steroids in both animal and human studies.

The mixed response of diverse forms of ocular inflammation studied within this brief series, and the different responses obtained within the same lesion group, make possible the existence of a varying degree of responsiveness of human lesion types to synthetic steroid therapy. Significant also is the report of a condition, presumably representing increased tissue tolerance to prednisone therapy, following long-term treatment. The presentation of a case of rheumatoid iritis and arthritis, with reactivation of the ocular lesion while on daily prednisone therapy, has given rise to this thought (Case 1, Table 3).

SUMMARY

An evaluation of prednisone for what it is, as well as for what it is not, gives rise to the following initial observations:

1. Prednisone represents an advance in steroid therapy to the extent that its effect on responsive acute ocular inflammation, both animal and human, shows a response equal to that obtained with other steroids in five times its dose.

2. While preliminary studies on prednisone reveal no significant widening of the spectrum of inflammatory conditions benefited by such therapy, there are recorded cases in this series responsive to prednisone whose history shows a failure to respond to previous steroid therapy. The adequacy of such previous treatment, however, is at times suspect. Further, there are patients in this series showing poor response to all steroids, including prednisone, one of whom showed a subsequent response to corticotropin. The possibility is thus raised that this represents a lesion-specific preference for human over synthetic steroid.

3. Acute anterior lesions responded best of all, as is the case in previous reports on all steroid therapy. Chronic iritis was the most refractory to treatment.

4. No significant side-effects were observed in patients treated daily for over three months with prednisone.

Dr. Ludwig von Sallmann reviewed this paper in manuscript.

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Ocular Toxoplasmosis

Clinical and Laboratory Diagnosis; Evaluation of Immunologic Tests; Treatment

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San Francisco

During December, 1954, the Parasitology and Tropical Medicine Study Section, Division of Research Grants, National Institutes of Health, sponsored a conference on granulomatous uveitis at the National Institutes of Health, Bethesda, Md., in order to determine the relationship of the various etiologic entities producing this form of uveitis. It was considered particularly desirable to evaluate the clinical and laboratory tests for the diagnosis of toxoplasmic infections of the eye and to determine whether these tests should be made available for the general use of ophthalmologists by the U. S. Public Health Service.

In addition to the author of this report, the following persons attended and presented data for consideration: Drs. Harry Feldman, Jack K. Frenkel, Alan Woods,* Hans Eichenwald, Ralph Ryan, Marion Brooks, and Ronald Wood. The following attended as observers and offered such information and advice as they considered desirable: Col. J. H. King (MC), U. S. Army; Capt. William Owen (MC), U. S. Army; Lieut. Col. Jack Passmore (MC), U. S. Army; Dr. Lorenz E. Zimmerman; Capt. Stephen J. Ryan (MC), U. S. N., and Lt. Cmdr. James C. Schumacher (MC), U. S. N.

MOTIVES IN CALLING THE CONFERENCE

A number of observers † had suspected for some years that toxoplasmosis as an acquired disease can cause an intraocular inflammation in adults. The discovery of organisms resembling Toxoplasma in 52 human eyes by Wilder ‡ and the isolation by Jacobs and co-workers [8] of Toxoplasma from a freshly enucleated human eye afflicted with chorioretinitis have in part confirmed this opinion.

These studies, and many other reports, have developed a considerable interest on the part of practicing ophthalmologists with regard to the relationship between Toxoplasma and uveitis. The resulting demand for serologic studies has increased beyond the capacity of presently established laboratories, most of which were organized for research purposes and not for the routine performance of tests. In addition, this demand has preceded the acquisition of clear-cut evidence as to the value of the immunologic tests in the diagnosis of ocular disease.

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Chairman's report of a conference held at Bethesda, Md., Dec. 13, 1954.

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* Dr. Alan Woods was unable to attend due to illness. Some of his data were presented by Dr. Ronald Wood.

† References 1-5.

‡ References 6 and 7.

Those in charge of laboratories carrying out the tests have had to provide information on the interpretation and value of the tests in patients with eye diseases when these values have not been adequately assessed. All those closely connected with the problem have felt the inconclusiveness of present criteria for diagnosis of toxoplasmic chorioretinitis.

The Communicable Disease Center, Chamblee, Ga., performs tests only on suspected cases of congenital toxoplasmosis. This service was established in 1952 as the result of the recommendations of a previous conference conducted by the same Study Section and reported by Sabin, Eichenwald, Feldman, and Jacobs.[9] This conference did not recommend the testing of suspected cases of acquired ocular toxoplasmosis because at that time it was considered doubtful by many that an ocular form of the disease existed as a postnatally acquired entity.

At the present time, to accommodate ophthalmologists, a limited number of tests are being performed at several research laboratories throughout the country.

OBJECTIVES OF THE CONFERENCE

The Conference had for its objectives the following determinations:

1. Whether it might be possible to establish criteria which would aid in the diagnosis of cases of ocular toxoplasmosis by clinical examination.

2. Whether there are clinical or laboratory data on the frequency of ocular toxoplasmosis.

3. Whether serologic or other immunologic tests are sufficiently developed and of such value that they can be recommended as routine diagnostic aids in the study of patients with chorioretinitis, and whether these tests should be made available by the Communicable Disease Center.

4. What advice should be given to ophthalmologists as to the interpretation of immunologic tests in making a presumptive or probable etiologic diagnosis of ocular toxoplasmosis.

5. What the experience of the conferees has been with regard to therapy of suspected cases of ocular toxoplasmosis.

AGENDA

In order to accomplish the objectives of the conference, the following agendum was organized:

1. A general discussion on methods employed to establish the diagnosis of all types of granulomatous uveitis, and the relationship of toxoplasmosis to this problem. Most of the general discussion has been eliminated from the present report for purposes of brevity.

2. Presentation of material summarizing the immunologic findings in patients with suspected toxoplasmic uveitis. An attempt was made to answer the following questions:

   (*a*) Is there a combination of clinical and immunologic findings which renders the diagnosis of ocular toxoplasmosis reasonably certain?

   (*b*) What is the correlation of the results of the methylene blue dye test, skin test, and complement fixation test in patients with uveitis?

   (*c*) If these tests are to be recommended, how should they be used?

   (*d*) Is the skin test of value in routine surveys for ocular toxoplasmosis, and can it be recommended as a practical test?

   (*e*) What is the degree of usefulness of the dye test in the diagnosis of ocular toxoplasmosis, and what titers are considered of significance?

3. Presentation of results of the treatment of suspected cases of ocular toxoplasmosis.

I. Clinical Criteria

A. Congenital and Neonatal Ocular Toxoplasmosis.—A congenital or neonatal illness, accompanied by inflammatory lesions of the central nervous system and involvement of the eye or viscera, strongly suggests the diagnosis of congenital toxoplasmosis. When supported by characteristic serologic findings,[9] the diagnosis is reasonably certain. Woods and co-workers [10] and Eichenwald (this conference) indicated that it is possible for an infant having congenital toxoplasmosis to survive with healed chorioretinal lesions, and the lesions become reactivated at about the age of 8 to 20 years.

When reactivation of these lesions occurs, it may be accompanied by serologic changes suggesting an active toxoplasmic infection.

Eichenwald presented the results obtained in a series of 140 cases of congenital toxoplasmosis, of which 80% showed evidence of chorioretinitis. He observed that infants and children develop toxoplasmic infections which may follow a variety of subsequent courses. These were the basis for the following grouping:

(1) A group of children with healed chorioretinitis who had been followed six to seven years without recurrence of the ocular inflammation.

(2) A second group of children with healed lesions who relapsed at about the age of 4 years. These children usually showed cerebral calcifications. One child in this group had four relapses.

(3) A third group of infants, with acute systemic toxoplasmosis which showed no initial evidence of ocular involvement.

Of the series of 140 cases of congenital toxoplasmosis, 28, or 20%, did not show chorioretinitis at the time that the diagnosis was established (most prior to the age of one month; one as late as 3 months of age). In 6 of the 28 cases chorioretinitis developed subsequently, at ages ranging from 2 weeks to 6 months, and in 4 cases eye involvement eventually became bilateral. The lesions differed in no way from those usually described at birth.

Eichenwald found that the ocular infection became chronic, with a prolonged course, in those children surviving the acute phase. Four of the infants had an optic neuritis in association with an acute toxoplasmic cerebral inflammation.

B. Postnatally Acquired Ocular Toxoplasmosis.—It was concluded by the ophthalmologists present that the chorioretinal lesions which Toxoplasma produces usually do not differ significantly from those due to other causes. The observation was made, however, that acute and recurrent large foci of chorioretinal inflammation with heavy opacification of the vitreous were more characteristic of lesions believed to be toxoplasmic. Coincidental involvement of the sclera over equatorial foci is also suggestive, as are satellite lesions recurring around previous foci. In common with other causes of chorioretinitis, the diagnosis of toxoplasmosis is most frequently presumptive, and is made by exclusion of other diseases. This exclusion is often difficult or impossible.

Chorioretinitis has been observed in but one of the reported cases of proved or probable acquired acute systemic toxoplasmosis in adults and children.[11] The only proved case of acquired adult ocular toxoplasmosis is that reported by Jacobs and associates.[8] This patient suffered recurrent attacks of chorioretinitis for eight and one-half years. The eye was finally enucleated because of glaucoma and pain. Toxoplasmas were isolated from the uveal tract and demonstrated in experimental animals and in tissue cultures. They were also seen in tissue sections of the eye. The patient had low dye test titers in the serum prior to enucleation, but the titer

rose to 1 : 4096 after surgery and declined to 1 : 128 one week later. It was assumed the handling of the eye during surgery liberated antigen which caused a rise in antibody titer.

The 53 eyes reported by Wilder [7] all contained organisms identical with Toxoplasma, and Jacobs and associates [12] were able to trace 21 patients in this group and found positive dye-test reactions in all, mostly in low titer. Three of the patients, however, had a titer of 1 : 256 and one had 1 : 2048. The authors concluded that the serologic findings favored the opinion that the organisms seen in the eyes were actually toxoplasmas. Duke-Elder and associates [13] also reported a case in which the eye was enucleated and organisms morphologically resembling Toxoplasma were found in the chorioretinal lesion.

It is believed by most of the group that acquired ocular toxoplasmosis exists as an entity; the incidence of this form as a cause of chorioretinitis cannot be assessed. It is thought by Woods and associates [10] that toxoplasmosis could account for about 25% of cases of granulomatous uveitis, and Frenkel, at this conference, expressed the opinion that toxoplasmosis must be responsible for 50% of cases of chorioretinitis. Since the acquired disease cannot be diagnosed on the basis of clinical findings, the clinician is forced to depend upon the exclusion of other diseases plus laboratory tests to establish a presumptive diagnosis.

II. Laboratory Diagnosis

A. Congenital Ocular Toxoplasmosis.—In those babies acquiring the disease late in gestation and exhibiting signs at or near birth, the methylene blue dye test is a useful diagnostic tool. This test becomes positive within three weeks after birth, rises rapidly to a fairly high titer, and persists at a reasonably high level for at least three years. The complement fixation test frequently becomes positive four to six weeks after infection, rapidly rises to a fairly high titer, and persists, in diminishing titer, for two to four years.[14] The combination of the clinical findings previously mentioned and the serologic data is strongly presumptive evidence that the disease is due to Toxoplasma.

B. Postnatally Acquired Ocular Toxoplasmosis.—Iridocyclitis may be associated as a spill-over from the posterior ocular inflammation, but up to the present time organisms have not been demonstrated in the anterior uvea.

In the reported cases of ocular toxoplasmosis the findings indicate that the chorioretinal lesions are usually fairly large. Other cases, reported by Hogan and co-workers,[15] had suggestive ocular findings in association with possibly significant changes in titer. The cases described by Wilder all had active chorioretinal lesions, mainly focal, often multiple, with extensive involvement and a tendency to recur.[7] The dye test titer in 21 of the cases which could be tested was generally low,[12] but the sera were not run at the time of surgery. It will be pointed out later that some participants felt that low titers were not inconsistent with a toxoplasmic etiology.

1. Skin Test: Frenkel [16] described the dermal hypersensitivity which occurs with Toxoplasma antigen produced from mouse peritoneal fluid, employing mouse spleen as a control. He showed that these antigens produce reactions of a delayed (tuberculin) type and later [4] described results with the skin test in a series of uveitis cases. Seventy-one per cent of 28 young patients with chorioretinitis had positive tests, whereas only 33% of 40 young patients with anterior uveitis had positive tests and only 10% of 50 young normal subjects had positive tests. Sabin

and associates [9] and Feldman [17] later indicated that the toxoplasmin skin test is of value in population surveys to determine the incidence of past or active toxoplasmosis in various age groups and geographic areas. Evidence was not at hand, at that time, nor is it presently available, as to the lack of specificity of the skin test antigen and the presence or absence of cross reactions with other organisms. Assuming that there is no cross reaction, a positive skin test is of value to the extent that it indicates exposure to Toxoplasma. If the test is negative, it suggests that the disease in question may not be toxoplasmic. Evidence will be presented subsequently to qualify these statements.

At this conference, Jacobs thought the skin test antigen might be standardized, possibly on the basis of its content of protein nitrogen or in relation to its optimal concentration as a complement-fixing antigen.

Frenkel stated that the mouse peritoneal fluid antigen was better because of its higher specific antigenicity; Toxoplasma could be concentrated by centrifugation, a procedure which would not be practicable with chorioallantoic membrane antigen. He also felt that mouse spleen was an adequate control for mouse protein. He found very few patients who reacted to the mouse control antigen and many that did with the chorioallantoic control antigen. Jacobs felt the very few false-positive results obtained with peritoneal exudate antigen supported this conclusion. He also felt the spleen control to be adequate.

Feldman stated that his experience was limited to the skin test antigen prepared from infected chorioallantoic membrane standardized to contain 2 complement-fixing units per dose. The control for this skin test is uninfected chorioallantoic membrane. He felt that egg antigen offered a better control than is available for antigen prepared from mouse peritoneal fluid. A positive test with his antigen consisted of induration of 10 mm. or more, with a negative control.

Hogan reported the results of skin tests employing the mouse peritoneal fluid antigen of Eli Lilly & Company and an antigen supplied by Jacobs. In 17 of 18 tests the results correlated, indicating that the two antigens were similar in their reactions; however, a larger series of patients would be required to arrive at adequate comparisons. Of his 206 patients with chorioretinitis, the skin test was positive in 36%. This figure may be compared with the 17% of positive skin tests in 379 cases of iridocyclitis. Therefore, it is found that a significant difference exists between the percentage of positive skin tests in the chorioretinitis group and that in the iridocyclitis group.

Feldman stated one could not generalize with regard to the incidence of positive tests because of the tremendous variation in frequency of positive reactors in different cities, states, and even countries. He indicated that two out of three people in the 30- to 40-age group had positive skin tests in some areas and felt that no time was to be saved by doing routine skin tests for the diagnosis of toxoplasmic uveitis because a negative skin test does not preclude the presence of serum antibodies. Feldman urged great care in the use of syringes, to be sure there is no trace of antigen in the control syringe, and in the performance of strictly intracutaneous inoculations.

Frenkel stated that he would be willing to accept an induration of 5 to 6 mm. with erythema of 10 to 20 mm. as a positive skin test in the absence of reaction at the control site. He presented evidence that skin testing causes a significant anamnestic rise in the dye test titer of many persons. Jacobs and Feldman had not observed such changes, using different antigens and/or time intervals.

Frenkel found that of a total of 39 patients with chorioretinitis, 64% were toxoplasmin-positive and 72% were positive with either the skin or the dye test; 91% of the patients with positive dye tests had positive skin tests. He felt that chorioretinitis could be diagnosed by means of a skin test (provided the skin test antigen was properly prepared) with an accuracy of 90% as compared with the dye test. In an area where the incidence of toxoplasmin sensitivity in an age control group is about 10% and that in a chorioretinitis group is 70%, he concluded that in about 63% of patients the eye lesions could be due to toxoplasmosis. No statement could be made, however, about any individual case.

Jacobs studied 353 patients with uveitis by means of dye and skin tests. For the skin test he used mouse peritoneal fluid antigen, with a spleen control, prepared freshly in his own laboratory. Good correlation was established between the skin and the dye test in cases of chorioretinitis, although, according to his findings, approximately 8.5% of the patients with negative dye tests had positive or "doubtful" skin tests. He reported that some patients studied over a long period of time had shown occasional negative dye tests. Such a phenomenon might account for the occasional positive skin test unsupported by the dye test.

Passmore stated that if one accepted 5 mm. of induration as a positive skin test, one obtained a higher correlation of skin and dye tests. He reported one patient who had a positive skin test and a negative dye test.

Jacobs felt that it might be feasible to substitute the skin for the dye test as the preliminary test in the routine diagnosis of ocular toxoplasmosis. If the skin test were found to be negative, a dye test could be carried out.

Frenkel reported on 163 patients, summarizing the results of dye, complement fixation, and skin tests.§ For the skin test toxoplasmic mouse peritoneal fluid with a mouse spleen control was used. The criterion for positive skin tests was 10 mm. of induration at the test site with absence of induration at the control site. In general he found good correlation between the skin and the dye tests.

Hogan presented the results of 617 cases of uveitis of all types. Of these, the dye test was positive in 32.1% and the skin test was positive in 22.9%. Of the 617 cases, 57 (9.2%) had positive skin tests and negative dye tests. On rechecking these findings, it was found that titers of less than 1 : 16 were not done on the sera tested. If all dilutions had been tested, the percentage of correlation of skin and dye tests might have been higher.

Gard [18] found good general agreement between skin and serologic tests, but observed that in about 10% of serologically positive cases the skin test was negative. Feldman,[19] using his antigen, found approximately 25% of adults with negative skin tests to have significant amounts of dye test antibody.

2. Methylene Blue Dye Test: Prior to 1948 the rabbit skin neutralization test was used to detect antibody in the serum of patients suspected of having toxoplasmosis. In 1948 Sabin and Feldman [20] described the methylene blue dye test, which has become the standard serologic test for the diagnosis of this disease. It uses alkaline methylene blue as an indication of the effect of antibody on Toxoplasma and appears to be specific. The highest dilution of serum in which 50% or more of the parasites remain unstained by the dye is considered to be the end-point, or titer, of that serum. The test has been utilized by many observers for the detection and study of human and experimental infections and has proved itself to be highly

§ These studies will be published in the *Acta* of the XVII International Ophthalmological Congress.

reliable. However, recent work by Muhlpfordt [21] and Awad,[22] to be discussed later, suggests a possible lack of specificity of this test.

Another serologic test is the complement fixation test, which utilizes antigen prepared from mouse peritoneal fluid or from the chorioallantois of chicks.‖ The different rates at which dye and complement fixation tests become positive may be used to advantage for diagnostic procedures. Infants born with active infections usually have dye test antibody in high titer soon after birth and have negative complement fixation tests. Subsequently the complement fixation test will become positive. Mothers of these infants ordinarily have high titers in both the complement fixation and the dye test. A high methylene blue dye test titer combined with a negative complement fixation test in older children and adults may mean either that the infection was acquired some time in the past and that the complement fixation test is no longer positive, or that the infection is active but the test is not yet positive.

Sabin and associates [9] indicated that a large proportion of the normal adult population have positive dye tests. The incidence increases up to 50% or more with increasing age in some localities, but rarely is the titer in excess of 1:64. These findings have been duplicated in various parts of the United States.[19] The reason for such a high incidence of positive tests in adults is unknown, but presumably many subclinical or unrecognized toxoplasmic infections occur. Siim [24] reported a series of young patients with fever, generalized lymph node enlargement, and other clinical features of infectious mononucleosis who had definite serologic evidence of a toxoplasmic infection. Subsequent cases of this type have been reported.¶ Pinkerton and Henderson,[28] Kass and associates,[29] and Skipper and colleagues [27] have reported cases of human toxoplasmosis which resembled a Rickettsial infection.

These reports would seemingly indicate that it is possible for humans to acquire toxoplasmosis in one of these, or even a milder, form and the disease be unrecognized. It must be these cases of undiagnosed infections that eventually lead to the cases of toxoplasmic chorioretinal inflammations.

Dr. Alan Woods and co-workers [10] studied 191 adult patients with granulomatous uveitis. Ten cases were instances of latent or chronic congenital toxoplasmosis with late exacerbations. Six other cases, possibly also representing late exacerbations of congenital infection, were found in patients 8 to 20 years of age. Of 78 cases of undetermined etiology, 44 had positive dye tests. In 42 of these 44 cases an explanation for a toxoplasmic etiology could be made. Woods feels that in clinical groups there were two types of ocular infection: one with a chronic course and low serum titer; the other with an acute course and rapidly rising titer.

Frenkel felt a presumptive diagnosis could be made with a positive skin test or qualitative dye test (titer of at least 1:16) in a large per cent of cases. Since skin test-dye test correlations were likewise good, either test could be used with advantage.

Jacobs indicated that he felt the importance of the dye test in establishing a diagnosis of ocular toxoplasmosis lay only in whether it was positive or negative, not in the titer reached. Therefore, because of the good correlation of the dye and skin tests, he felt it was possible to recommend the skin test in place of the dye test in order to eliminate the expense and time involved in doing routine dye tests as a primary procedure. He did not feel that preliminary skin testing would interfere with serologic testing at a later date, because if the skin test were read in 48 hours

‖ References 14 and 23.

¶ References 25-27.

and found negative, blood could be withdrawn at that time for the dye test and, according to him, before a possible anamnestic rise in antibodies might occur. He had tested many sera repeatedly and found but little variation in titer, although occasional sera fluctuated a significant amount. He stated there was no way to stipulate that certain titers are diagnostic in relation to ocular disease.

Feldman found the dye test antibody in children remained at a high level for a considerable period, a finding which is significant as far as the diagnosis of childhood toxoplasmosis is concerned. As a result of routine surveys, he had found a tremendous variation in the incidence of positive dye tests in this country and various sections of the world; for example, 4% of Navajo Indians have positive tests in a titer of 1:16 or more, as compared with 63% to 70% of subjects in Honduras and Tahiti. He indicated that the presence of antibody in the blood was not necessarily evidence of a chronic infection in the patient.

Hogan found 32.1% of positive dye tests in a titer of 1:16 or more in 617 patients with all forms of uveitis. It was found that the patients with chorioretinitis had a higher incidence of positive tests (48%) than those with iridocyclitis (24%). This higher incidence of positive tests might be evidence for recommending the routine use of tests in such cases. There also seemed to be a correlation between the intensity of the chorioretinal inflammation and the height of the titer in a fair number of cases, although this finding needs further elaboration.

Ryan reported on 39 cases of presumptive toxoplasmic uveitis out of 67 patients with granulomatous uveitis. Of the 39 patients, 37 were adult and therefore were presumed to have acquired toxoplasmosis postnatally; 2 presumably acquired the infection prenatally. This group of patients had negative studies for other etiologic agents as the cause of the uveitis, and the diagnosis was made on the basis of the dye test.

Muhlpfordt [21] found that guinea pigs, rats, and golden hamsters could be fed one feeding of Sarcocystis and develop positive titers for toxoplasmosis, which persisted for considerable periods. Awad [22] found that sera of mice and rabbits inoculated with Trichomonas vaginalis and Sarcocystis gave cross reactions in the dye test. Similar findings were observed in mice having recovered from an infection with Trypanosoma cruzi. A patient, however, in whom Sarcocystis infection was proved by biopsy had negative dye and complement fixation tests using Toxoplasma antigen.[30] These observations may indicate the lack of specificity of the dye test for the diagnosis of toxoplasmosis, but the observed titers and other aspects of this report should probably be repeated. However, these reports do demonstrate the necessity of pursuing additional investigations as to the specificity and other aspects of the methylene blue dye test.

3. Biopsy: In active systemic infections, a diagnosis of toxoplasmosis can be made by removing an enlarged lymph node for culture and study of microscopic sections,# or by muscle biopsy.[29] Organisms have been recovered by inoculation with ground-up lymph node or muscle tissue of experimental animals and of the chorioallantoic membrane of eggs.* This method of establishing the diagnosis should not be overlooked in patients with muscular or lymph node involvement during an acute systemic illness. A negative result does not rule out toxoplasmosis, and the procedure could be expected to fail in most cases of chronic ocular disease.

References 26, 31 and 32.

* References 26, 29, and 31.

4. Complement Fixation Test: Most of the participants in this conference were agreed that the complement fixation test was of little value in helping to establish the diagnosis in patients with uveitis, except for infants with congenital toxoplasmic chorioretinitis. Much more remains to be done with this test before a definite conclusion can be drawn.

TREATMENT

Warren and Sabin [33] tested a large number of antiprotozoal drugs and chemotherapeutic agents for their in vitro and in vivo effectiveness against Toxoplasma and found that sulfonamide compounds were the most active. Almost all investigators have found that the sulfonamides are active, but great differences in the degree of activity have been observed.† This may be due to varying doses of organisms, methods of inoculation, variation in strains, and host susceptibility. Eyles and Coleman [39] found sulfadiazine, sulfamerazine, and sulfamethazine to be more effective at lower dosage than the other sulfonamide compounds when tested under experimental conditions in mice. Clinical studies in human patients treated with sulfadiazine for acute toxoplasmosis have been disappointing.‡ Sulfonamides have been administered in some congenital cases, but the therapeutic results are difficult to evaluate because most of the cases had progressed to the subacute or chronic stage.

The sulfones have been shown to have anti-Toxoplasma activity,§ but Eyles [43] has shown that sulfadiazine is superior in its effects when tested under experimental conditions. Since most of the sulfones are as toxic as, or more toxic than, sulfadiazine, he concluded that this sulfonamide was superior to any of the sulfones tested. Beverley and associates [42] reported satisfactory results in experimental ocular infection employing diaminodiphenylsulfone (D. D. S.).

None of the antibiotics which have been tested appear to have a marked effect against Toxoplasma.

The 2,4′-diaminopyrimidines appear to offer the most promise in the treatment of experimental infections, especially when combined with sulfadiazine. The best appears to be pyrimethamine (2,4′-diamino-5-[4′-chlorophenyl]-6-ethyl pyrimidine; Daraprim), manufactured by Burroughs Wellcome & Company, Inc. This compound was originally developed for its antimalarial activity, and its effectiveness against Toxoplasma was reported simultaneously by Summers [41] and Eyles and Coleman.[44] The use of pyrimethamine in experimental infections was found to be superior to that of sulfonamides, and it was observed by Eyles and Coleman that a late recurrence of parasitic activity was almost always absent. Most of the treated mice which survived for two to three weeks were cured. The effective doses of pyrimethamine, however, approached the toxic level, so that Eyles [43] searched for a combination of drugs which would be effective. He soon discovered that sulfadiazine acts synergistically with pyrimethamine, allowing the use of much smaller dose of each to control the experimental infections.

The use of pyrimethamine and sulfadiazine in the treatment of human cases must be carried out with caution. Experimental studies show that pyrimethamine produces a megaloblastic change in the red cell precursors in the bone marrow, and an inhibition of leucopoiesis, causing anemia and leucopenia. Also, gastrointestinal

† References 34-38.

‡ References 29 and 40.

§ References 41 and 42.

side-effects are common. The usual precautions must be taken during the administration of sulfadiazine.

Most ophthalmologists in this country who have been interested in the problem of ocular toxoplasmosis have treated suspicious chorioretinitis cases with pyrimethamine and sulfadiazine. Our clinic has customarily given 25 mg. of pyrimethamine three times a day and 4 gm. of sulfadiazine a day. Treatment is continued for two to three weeks, the patient being constantly watched for signs of toxicity. We found improvement in 2 of 15 cases so treated.

Ryan [45] treated a series of suspected cases of granulomatous chorioretinitis with 25 to 75 mg. of pyrimethamine in combination with 30 mg. per kilogram of sulfadiazine per day. Eight of twenty-nine suspected cases definitely responded.

Eichenwald stated that he had used pyrimethamine and sulfadiazine in a small number of cases of toxoplasmosis without improvement.

Frenkel reported rapid healing in one, slow healing in two, and no significant response in one case treated with approximately 25 mg. of pyrimethamine and 2 to 4 gm. of sulfadiazine daily. He stated that much of the difficulty in evaluating treatment was inherent in the lack of adequate controls; since there was variation in the severity of cases, one could not predict their outcome with or without treatment. He also referred to the dual pathogenesis of lesions, those due to cyst rupture, and those due to the proliferative forms of Toxoplasma. Only the latter could be expected to respond to chemotherapy. Frenkel stated that the most important side-effect of treatment was a lowering of the platelet count, which could be reversed by the administration of folic acid. Cortisone and other corticoids were contraindicated, since systemic administration has led to reactivation of latent chronic infection in animals and appears to have been the cause of death in one patient.

Passmore stated that one of five patients was improved on treatment with 50 mg. of pyrimethamine and 4 gm. of sulfadiazine daily for four weeks.

Feldman made the statement that the combination of pyrimethamine and sulfadiazine might cause remissions in the disease in any patient with an infectious type of uveitis. Therefore a therapeutic response is not necessarily an indicator of a specific effect against Toxoplasma.

Dr. Eichenwald indicated that corticotropin given to children often caused a remission of the signs, but cessation of treatment seemed always to be followed by a relapse.

SUMMARY AND CONCLUSIONS

Ordinarily it is not possible on the basis of the clinical ocular findings to make a presumptive diagnosis of toxoplasmosis. However, there is suggestive evidence, on the basis of the few reported cases, that large or multiple areas of chorioretinitis are more frequently associated with this type of infection, especially those associated with scleral involvement.

The value of the immunologic tests as summarized by the findings of this conference indicates that the dye test is positive in a titer of 1 : 16 or more in approximately 40% of patients with all types of uveitis and that the incidence of positive tests is higher in patients with chorioretinitis (50%-60%) than in those with iridocyclitis (30%). The latter figure is about that found in the normal population in many parts of the United States. The level of titer found in most patients was of a low order (usually less than 1 : 256). This finding makes the interpretation of dye test results difficult. None of the conferees was willing to accept any specific

titer level above which one might establish a probable diagnosis. Jacobs and Frenkel felt that the qualitative outcome of the dye test was the important datum in most cases. Others (Feldman and Hogan) felt that changes of titer in a significant amount (at least a fourfold dilution) might be considered as indicating a probable diagnosis. However, it was also pointed out that such a titer change is rarely observed.

It was not possible to decide whether a negative dye test might rule out toxoplasmosis, except that in children under age 10 a negative test can be considered as quite significant.

Most participants felt that there was good correlation between the findings of the skin and dye tests.

Most participants felt the skin test alone was not sufficiently developed to establish the diagnosis of toxoplasmic uveitis. The variation in antigen preparations, types of antigens, standardization, and interpretation of positive and negative tests suggested that additional studies would be necessary before a skin test could be recommended. Frenkel and Jacobs felt that the test was at least an adequate screening device.

The complement fixation test was felt to be of no particular value in the diagnosis of ocular toxoplasmosis, although it would be of considerable value if a change from a negative to a positive result occurred. Aside from congenital cases, however, most studies on uveitis patients have failed to show such a change.

On the basis of the findings reported by the various observers, it was concluded that a very accurate estimate of the frequency of acquired ocular toxoplasmosis could not be made. Further detailed investigation by close coordination of clinical and laboratory observations will be required to refine the methods used to arrive at probable diagnoses.

Therapy of suspected cases of toxoplasmic uveitis with sulfadiazine alone and combined with pyrimethamine (Daraprim) have showed markedly varying results. One carefully studied group of cases showed some lesions to respond well to sulfadiazine and pyrimethamine. Considerable additional work will be necessary before the results of treatment of human cases will be known.

RECOMMENDATIONS MADE BY THE CONFERENCE

The panel voted against recommending the establishment of a routine Public Health service to ophthalmologists and others for processing sera of patients with suspected uveitis. The final vote was eight against and two for. Six of the seven ophthalmologists present were against the establishment of such a service. Those voting against routine testing had the following reasons:

1. Sufficient information is not available to enable one to tell the referring ophthalmologists whether a specific titer is of any significance.

2. Insufficient work has been done on improvement and standardization of the tests; therefore they are still a research laboratory procedure.

3. Serial testing of sera would often prove impractical and too expensive, and a single test would be of little value to the referring ophthalmologist.

4. Insufficient information is available on correlation of dye and skin tests, or on standardization of skin tests to permit recommendation of the use of dye tests on those patients having negative skin tests.

5. The specificity of the dye test for toxoplasmosis alone has not been established. At the same time, its nonspecificity has not been established.

Those conferees in favor of recommending routine testing of sera by the Communicable Disease Center for ophthalmologists had the following reasons:

1. Ophthalmologists in private and hospital practice request this service. The present research laboratories are incapable of satisfying the demand, and either object to the performance of routine diagnostic tests or require too long to perform them. Most state health laboratories lack qualified personnel to perform the dye test.

2. The incidence of positive dye tests is significantly higher in chorioretinitis patients, and therefore the tests could be reasonably recommended for such cases.

3. The correlation of dye and skin tests is close, and the skin test could be recommended as the initial test; if it is negative, serum could then be processed in all such cases, thus cutting down on the numbers of sera sent for testing.

4. It would make generally available to ophthalmologists a diagnostic and research tool which may stimulate research on a broader basis.

As a result of these divergences of opinion it was decided to avoid recommending routine testing, at least until present investigations are completed.

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Cataracts in Vitamin E Deficiency

An Experimental Study in the Turkey Embryo

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Nutritional deficiencies in relation to disorders of the eye have been described by many workers.* Cataracts in rats fed a riboflavin-deficient diet were described in 1931 by Day, Langston, and O'Brien.[3] Curtis and co-workers,[4] in 1932, produced cataracts in rats with a tryptophan-deficient diet. As far as we know, these are the only true primary deficiencies that have resulted in cataract formation.

The relation of vitamin E to retrolental fibroplasia was suggested by Owens and Owens [5] in 1939. Callison and Orent-Keiles,[6] in 1951, observed a lesion in embryos from rats fed vitamin E-deficient diets which suggested retrolental fibroplasia. Cataracts were described in 1954 by Ferguson, Atkinson, and Couch [7] in turkey embryos obtained from hens fed a practical-type diet low in vitamin E. A similar lesion has occurred in turkey embryos obtained from hens fed a synthetic-type diet deficient in vitamin E. The pathologic changes in these eyes are reported here.

EXPERIMENTAL PROCEDURE

Sixteen Beltsville Small White turkey hens were reared to maturity on a practical-type diet † and maintained in pens with raised wire floors. At maturity they were placed in individual laying cages and fed the following purified synthetic basal diet: 62% sucrose mixture, 24% Drackett C-1 assay protein, 3% fresh lard, 11% salts mixture, plus the following supplements added per kilogram of diet: 20 mg. of thiamine hydrochloride, 6 mg. of riboflavin, 15 mg. of calcium pantothenate, 100 mg. of nicotinamide, 30γ of cyanocobalamin U. S. P., 4 mg. of pyridoxine, 20 mg. of paraaminobenzoic acid, 100 mg. of inositol, 0.2 mg. of biotin, 2.0 mg. of folic acid, 0.5 mg. of menadione, 2000 mg. of choline chloride, 33 mg. of penicillin, 10,000 I. U. of vitamin A, 3800 I. C. U. of vitamin D_3, 7.5 mg. of methionine, and 4 gm. of aminoacetic acid. The salts mixture supplied the following constituents per kilogram of diet: 288 mg. of manganese, 30 mg. of iodine, 559 mg. of magnesium, 246 mg. of iron, 4.29 mg. of copper, 6.71 mg. of zinc, and 0.11 mg. of

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* References 1 and 2.

† References 7 and 8.

cobalt. Calcium, phosphorus, sodium chloride, and potassium were present in the salts mixture at the levels of 2.5%, 1.0%, 0.5%, and 0.2%, respectively.

Group I, consisting of eight birds, was fed the basal diet. Group II, also consisting of eight birds, was fed the basal diet plus vitamin E (*d*-α-tocopherol acetate, 20 mg./per pound of diet) for nine and one-half weeks, after which time the vitamin E was increased to 40 mg/per pound for the remainder of the 15 weeks of this experiment.

The hens were artificially inseminated at weekly intervals with pooled semen from Beltsville Small White toms. Eggs were collected daily, stored in a cooler at 55 C, and set at weekly intervals. Embryos were first removed on the fifth day of incubation. All specimens used for pathologic study were alive when they were taken from the eggs and were placed immediately in 4% formaldehyde solution U. S. P. Embryos from the fifth through the eighth day of incubation were preserved in toto. The body cavity of all other embryos from the 9th to the

Fig. 1.—Embryo 27 days of age. *A*, embryo from hen receiving vitamin E; *B*, embryo from hen on vitamin E-deficient diet, showing keratoconus.

28th day (hatching) was opened, and the eyes were punctured with a scalpel to facilitate fixation. The eyes were subsequently removed and prepared for either paraffin or celloidon embedding. Serial sections were stained routinely with hematoxylin and eosin. Select sections were stained by the following techniques: Masson's trichrome stain, Mallory's aniline blue and fast green, and von Kossa's calcium stain.

One hundred nine embryos were studied. A minimum of two embryos was collected from Groups I and II for each day of incubation after the fourth. Gross observations were made on the eyes of these embryos; an eye from at least one of the embryos for each day of the incubation period was studied histologically.

EXPERIMENTAL STUDY

One or both eyes from 109 embryos from vitamin E-deficient and normal turkeys, varying in age from the 5th through the 28th day of incubation, were studied. The deficient embryos showed a keratoconus-like change when 19 days of age (Fig. 1), which increased as the embryo aged. Hemorrhage within the eye was observed in two of the deficient embryos. Opacities varied in size in the

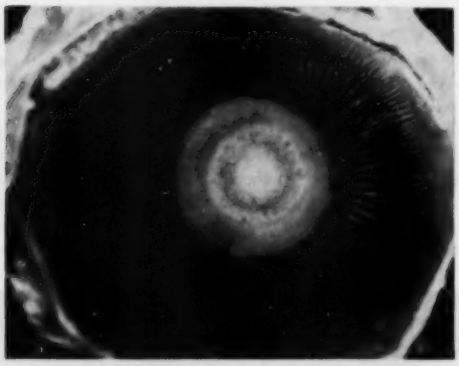


Fig. 2.—Embryo 31 H, 28 days of age. This hen was vitamin E-deficient. The lens is opaque. Photograph shows posterior surface of lens.

Fig. 3.—Embryo 1-5, 18 days of age. Degeneration of the lens immediately beneath the capsule. Note the large area in the cornea in which the cells are absent. Hematoxylin and eosin; × 32.

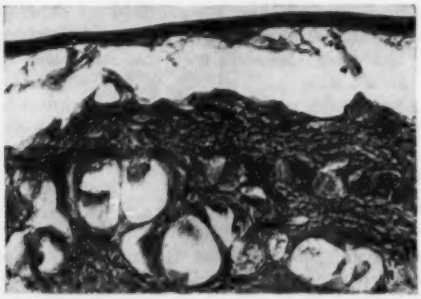


Fig. 4.—Embryo same as that in Figure 3. Focal areas of degeneration in the lens, showing Morgagni bodies. Hematoxylin and eosin; reduced to about 76% of mag. × 250.

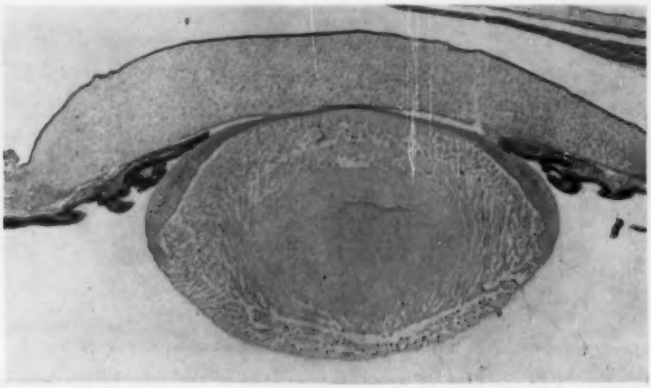


Fig. 5.—Embryo 3-4, 20 days of age. There is a large mass of relatively well-preserved lens protein, surrounded by a zone of degenerating protein. Hematoxylin and eosin; × 25.

deficient embryos (Fig. 2); however, the two eyes were usually similar in the same bird. There were opacities in one or both eyes of 21 in the group of 54 vitamin E-deficient embryos. Only 2 embryos with opacities were observed in 55 turkeys from the vitamin E-supplemented group.

Lens.—The most conspicuous change present in the eyes of these embryos occurred in the lens. It was characterized by the liquefaction of either a part or essentially all of the lens protein. The earliest changes were small focal areas of liquefaction located either in the center or at the periphery of the lens immediately beneath the capsule (Fig. 3). These were considered as Morgagni bodies (Fig. 4).

The pattern of liquefaction of the lens varied. Sometimes a large mass of solid, protein-like material was present in the center of the lens, completely surrounded either by a zone of degenerating protein or by liquid material (Fig. 5). In other specimens a similar mass of well-preserved lens protein was present near the periphery. A blue-staining, slightly granular material was present in focal areas in some of these degenerating lenses. This gave a positive staining reaction for calcium. Cellular debris was infrequent within these degenerating lenses.

Fig. 6.—Embryo 7-6, 24 days of age. There is a decrease in the anterior-posterior diameter when the lens is almost completely liquid. Hematoxylin and eosin; × 32.

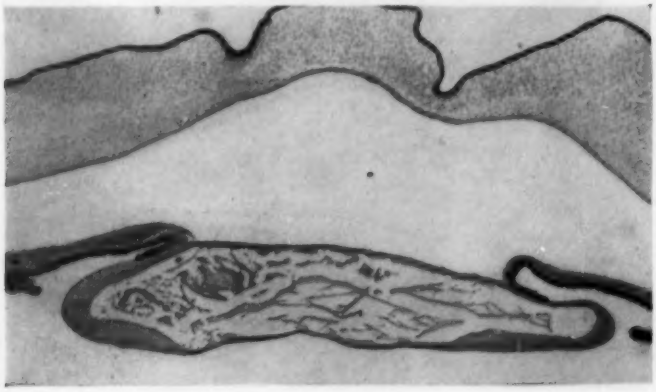
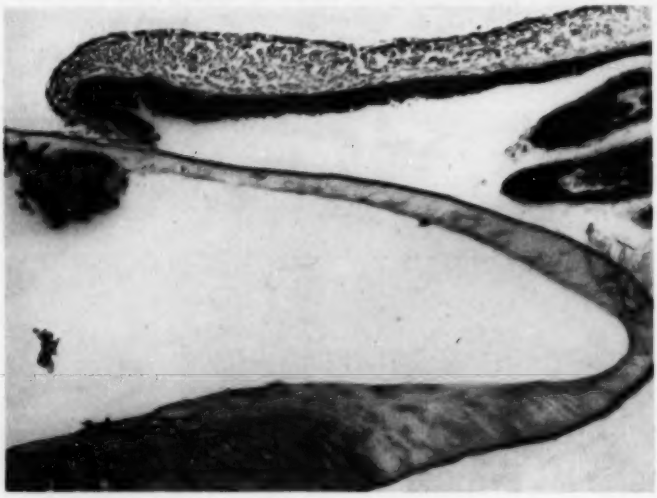


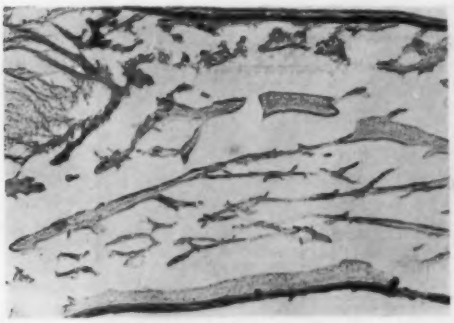
Fig. 7.—Embryo 1-29, 23 days of age. Degeneration of the cells in the lens epithelium; hyperplasia of these same cells. Note the extensive degeneration of the lens protein. Hematoxylin and eosin; reduced to about 76% of mag. × 120.

The capsule appeared normal, even though the lens was essentially liquid. The size of the lens usually was affected little by this degenerative process (Fig. 5). There did occur a decrease in the anterior-posterior diameter in some of the lenses when the protein was extensively liquefied (Fig. 6). The distance between the lateral margins of the lens did not appear to be significantly affected.

Lens Epithelium.—Epithelial cells normally cover the anterior portion of the lens of the turkey's eye and are absent on the posterior surface. No changes were observed in the lens epithelium in those eyes where the amount of liquefaction was minimal. Only in embryos with the most extensive lesions were there significant changes in these cells. In the latter the epithelial cells varied widely in both size and shape; some had large vacuoles within their cytoplasm (Fig. 7), while the nuclei of other cells were pyknotic. Degeneration and focal areas of proliferation of the epithelial cells were conspicuous along the anterior surface of the lens in

Fig. 8.—Embryo W-1, 28 days of age. Proliferation of epithelial cells along the anterior surface of the lens; calcium deposits in this group of cells. Von Kossa's stain; × 150.





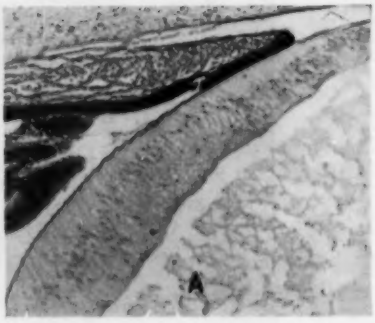


Fig. 9.—Embryo 7-26, 24 days of age. A narrow zone of epithelial cells is present along the posterior surface of this lens. The lens protein has degenerated. Hematoxylin and eosin; reduced to 76% of mag. × 150.

Fig. 10.—Embryo 3-4, 20 days of age. Few changes are present in lens epithelium. The lens protein is completely degenerated. A few pyknotic nuclei in the secondary lens fibers may be seen at *A*. Hematoxylin and eosin; reduced to 82% of mag. × 150.

some of the embryos (Fig. 8). In some specimens with extensive degeneration, epithelial cells were continuous along the posterior surface of the lens (Fig. 9).

Lens Fibers.—The primary and secondary lens fibers appeared normal in those eyes where the lens showed only focal areas of liquefaction (Figs. 3 and 5). Sometimes the secondary lens fibers were distorted by cyst-like areas occurring between the fibers. As the degree of liquefaction progressed, the nuclei of these fibers became pyknotic, and subsequently the entire cell completely disappeared (Figs. 6, 10, and 11). The nuclei of the secondary lens fibers adjacent to the lens epithelium seemed to be better preserved and persisted for a longer time than those fibers in the center of the lens. Sometimes a large number of degenerating fibers were surrounded by liquefying protein (Fig. 5).

Cornea.—Opaque spots were observed macroscopically in the cornea of six of the vitamin E-deficient embryos and in only one from the vitamin E-supplemented group. Microscopically, there were variations in the width of the cornea even within the same microscopic field (Figs. 6 and 12). This was accompanied by

Fig. 11.—Embryo 10-31, 18 days of age. This bird was given a supplement of vitamin E. This lens is a normal one for comparison with the lens shown in Figure 10. Hematoxylin and eosin; reduced to 82% of mag. × 150.

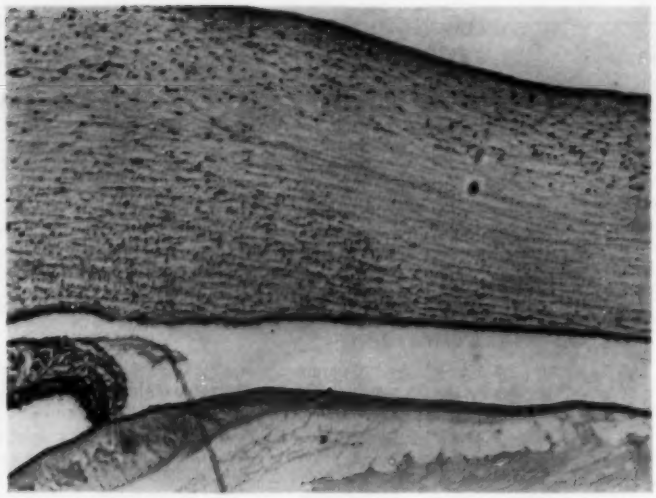


Fig. 12.—Embryo 1-5, 18 days of age. The cells are absent in focal areas of the cornea. Note the degeneration of the lens. Hematoxylin and eosin; × 150.

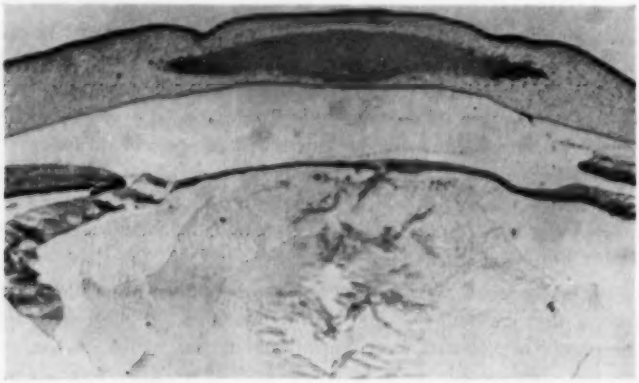


Fig. 13.—Embryo 21 E, 28 days of age. The lens protein is completely degenerated. A large area in the cornea is infiltrated with granules of blue-staining material that gives a positive reaction for calcium. Hematoxylin and eosin; × 36.

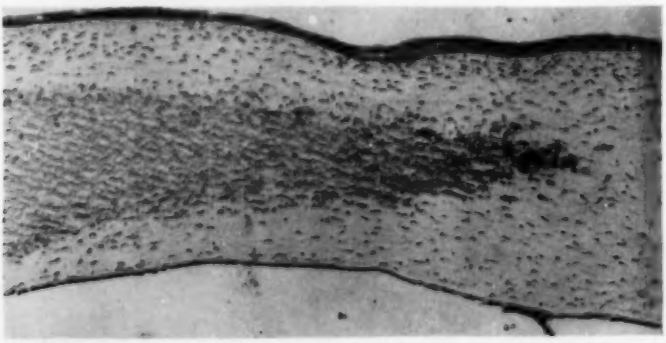


Fig. 14.—Embryo same as that in Figure 13. Note the absence of cells in the cornea around the deposit of calcium. Hematoxylin and eosin; × 150.

a variation in the distribution of cells, probably due to differences in the water content of the cornea. In fact, in many of these deficient embryos there was a complete absence of cells within focal areas of the cornea (Figs. 3 and 12). A blue-staining granular material giving a positive staining reaction for calcium was present in the cornea of a few of the embryos (Figs. 13 and 14).

The epithelial cells covering the cornea usually appeared normal; however, a few showed either areas of degeneration or proliferation of these cells (Fig. 15). Usually the endothelial cells were intact and appeared normal, although in a few birds there was a complete absence of these cells in focal areas (Fig. 15).

In four embryos the lens was fused to the posterior surface of the iris, and in one a few inflammatory cells infiltrated the area. In all the other birds no inflammatory reaction was observed in any part of the eye.

An occasional turkey hatched from the vitamin E-deficient group of hens has shown cataracts. Data are not available at this time to show how frequently this occurs.

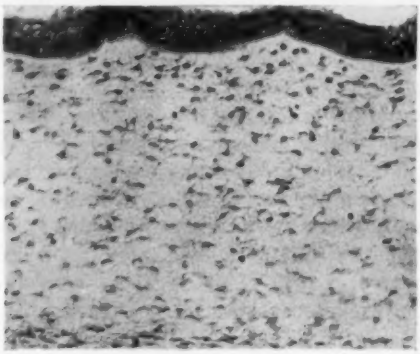


Fig. 15.—Embryo 7-15, 27 days of age. Hyperplasia has occurred in the epithelial cells covering the cornea. The endothelial cells are absent in this area. Hematoxylin and eosin; reduced to 80% of mag. × 240.

COMMENT

Friedenwald,[9] in 1929, stated that the ways in which the lens can respond to injury are limited to three. These are as follows: 1. The cells may die slowly and become sclerosed. 2. When the lens fibers die more rapidly, they become autolysed and from the resulting fluid various constituents are precipitated, either amorphously or in the form of crystals. 3. The only cells in the lens capable of regenerative activity are those of the subcapsular epithelium. In response to mild injury these cells proliferate, sometimes forming a dense opaque membrane, many cells deep. The changes occurring in the lens of the vitamin E-deficient turkey embryos represent the last two processes, as described by Friedenwald.

It would seem from this study that the lens protein, after formation, liquefies. This degeneration, of course, is a chemical one, which begins in focal areas and progresses until all the lens protein may become liquid. This opinion is based upon the observation that masses of relatively well-preserved lenses are completely surrounded by a semiliquid medium (Fig. 4). If the lens protein was abnormal at the time of formation, one might expect a similar consistency of the entire lens. Furthermore, the earliest changes observed within a lens are small cyst-like areas of degeneration, many of which are present beneath the capsule (Fig. 3). The

continuity of the lenses is relatively well preserved even in those cases where the protein is completely liquefied (Fig. 5).

It is suggested that the chemical composition of the aqueous humor may be affected by the metabolic products that diffuse through the lens capsule from the degenerating lens protein. These metabolic products may be related to the swelling of the eye. Since fluid within the anterior chamber diffuses through the posterior endothelial layer of cells in the cornea, it is likely that the edema of the cornea and the degeneration of these cells are secondary to the changes in the lens protein. However, since there is no consistent correlation between the extent of degeneration in the lens and the changes in the cornea, it might be that the lesions in the cornea develop independently of those in the lens.

Degenerative changes in the primary and secondary lens fibers seem to follow, rather than precede, the liquefaction of the lens protein. Extensive degeneration and proliferation of the lens epithelial cells occur only in those cases where the lens is extensively degenerated. It is of interest also to recall that in many cases the lens protein appeared normal and subsequently degenerated.

There is a wide variation in the pathologic changes in the lens and cornea of the deficient embryos. An occasional embryo from the same group of hens used for these histologic studies, when permitted to hatch, has shown cataracts. Such turkeys appear to be normal except for the cataracts. Edema of the cornea and a few small cyst-like areas within the lenses occurred in a few embryos from turkeys given a supplement of vitamin E. It cannot be said at this time whether such changes would have either progressed or regressed had the embryo been permitted to live. It was reported ‡ that the addition of vitamin E to the diet of the hen prevented eye lesion in the turkey embryo. The incidence of cataract in the embryo and the tocopherol content of the egg yolk were shown to be correlated. However, it was pointed out [8] that when the vitamin-E treatments were reversed, at the end of nine weeks, the incidence of cataract decreased to zero two weeks later. At the end of the 17-week study, the tocopherol content was essentially as low in the eggs from the unsupplemented group as that found at the end of the first nine weeks; yet no eye lesions had been found during the 12th through the 17th week in any group. Similarly, the hatchability changes as a result of the reversal of vitamin-E treatments, and tocopherol analyses of the egg yolk were not as great as expected. It was suggested that an unidentified factor, acting independently or interacting with vitamin E, might account for this difference. Since the hens used in the present study had been reared on a diet which did not contain unidentified factor sources and such factors were not present in the synthetic diet, it is also possible in the present study that vitamin E is not the entire factor, but that this vitamin is the major factor in the prevention of cataract in the turkey embryo.

The turkey, like all vertebrates,[1] normally does not have any epithelium on the posterior surface of the lens. Epithelial cells have occurred, however, on the posterior surface of the lens in many of these vitamin E-deficient embryos. The presence of calcium within the degenerating lenses and in the cornea of these turkeys is interesting in view of the theory that Clark [10] has suggested for the etiology of certain cataracts. She has suggested that calcium ions enter the lens and combine with the protein. The lens then becomes sensitized, and, as a result

‡ References 7 and 8.

of the presence of ultraviolet light, the protein is denatured and precipitates. Our embryos showed the presence of calcium and cataracts without ever being in the presence of ultraviolet light.

SUMMARY

Turkey embryos obtained from vitamin E-deficient hens show extensive liquefaction of the lens protein and focal areas of degeneration in the cornea. The lens epithelium shows degeneration and proliferation when the lens protein is extensively degenerated. Sometimes epithelial cells are continuous along the posterior surface of the lens. From this study it would seem that the lens protein forms and subsequently liquefies. On occasion, turkeys permitted to hatch from these vitamin E-deficient hens have bilateral cataracts. There is nothing in this study to suggest the mechanism for these cataracts.

The histological material in this study was prepared by Mrs. M. S. Cross and Mrs. O. J. Hander.

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Miosis in Argyll Robertson Syndrome and Related Pupillary Disorders

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According to the classical description,* the Argyll Robertson syndrome is characterized by the following essential features: (1) the absence or diminution of the pupillary reflex to light; (2) an active or hyperactive pupillary contraction to near vision, and (3) the presence of miosis.

The cause of the miosis in the Argyll Robertson syndrome and in related pupillary disturbances has never been satisfactorily explained. In the abundant literature, extending over almost a century, two main theories have evolved:

1. The miosis is due to an interruption of the sympathetic dilator fibers.
2. The miosis is due to irritation within the parasympathetic reflex arc.

It is the purpose of this paper to discuss, on the basis of pupillographic and pharmacodynamic tests, the mechanism by which miosis is produced in the Argyll Robertson and related pupillary syndromes. An attempt will be made to clarify some of the basic problems which have perpetuated the controversies involved. The question of the probable anatomical site of the lesion in these conditions will not be discussed; this question will be the subject of a future publication.

I. METHODS

Pupillary diameter and reactions were recorded by pupillography, as previously described.† The general statements on pupillary innervation contained in this paper are based on the entire material collected in this laboratory. It includes approximately 2800 clinical cases with pupillary pathology of all kinds. In addition, about 300 normal human subjects were examined, most of them repeatedly and under various conditions. Animal experiments were done on monkeys, cats, rabbits, guinea pigs, rats, pigeons, chickens, frogs, and fish. Monkeys and cats were used most extensively. Each animal was examined many times both before and after experimental lesions were placed at specific sites within the centers and pathways of pupillary control. The statements concerning miosis are based on clinical pupillograms obtained from 126 patients who showed miosis as a part of the Argyll Robertson or related syndrome, as well as on pharmacodynamic experiments done on these patients and on normal human subjects and experimental animals.

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* References 1 and 2.

† References 3 to 6.

II. DEFINITION OF MIOSIS

Since the definition of miosis varies greatly from author to author, it is necessary to define the term. Some call a pupil miotic only when it is of pinpoint size; others, when it is but slightly smaller than normal. But even the statements on what constitutes "normal" pupillary size vary. Since the size of the normal pupil varies with the intensity of illumination, the degree of near vision, the emotional status of the subject, the age of the subject, and other factors, any statement involving pupillary size can be meaningful only when the conditions under which the measurements were taken are specified.

We have found it best to study the pupils after at least six minutes of dark adaptation. Sitting in a comfortable chair, equipped with headrest and chinrest, the patient looks at a small red point of light about 15 degrees above the horizontal and at a distance of 10 ft. from his eyes. It is important that disturbing sensory or emotional stimuli be excluded.

Under these experimental conditions, the variability according to age was found to be less than is generally assumed (Table 1).

The values contained in Table 1 may seem surprisingly large to those accustomed to examining the pupils in light. It is, therefore, emphasized that they apply to

TABLE 1.—*Approximate Values for Pupillary Diameter in Healthy Persons According to Age, After at Least Six Minutes of Dark Adaptation*

Age, Yr.	Pupillary Size in Darkness, Mm.
5-10	7.0-9.0
10-20	7.0-9.0
20-30	7.0-8.7
30-40	7.0-8.5
40-50	6.8-8.0
50-60	6.5-8.0
60-70	5.8-7.5
70-80	5.5-7.5

the dark-adapted pupil. Our values are from 1 to 3 mm. larger than the ones which had been determined during the clinical examination in the same patient.

Since a person below 70 years of age should, under our experimental conditions, have pupils of no less than 5.8 mm. diameter, we have arbitrarily termed "miotic" pupils which show a diameter of less than 5.0 mm. after adaptation to darkness.

III. MECHANISMS OF MIOSIS

Sympathetic impulses dilate the pupil, and parasympathetic impulses contract it. It follows that miosis may be due to parasympathetic hyperactivity or to lack of sympathetic innervation. This statement oversimplifies reality, since four mechanisms for the production of miosis must be considered.

1. Parasympathetic hyperactivity may be due to an irritative process within the parasympathetic reflex arc, leading to an abnormal increase in sphincter tonus.

2. Weakened dilator impulses due to lesions in the peripheral sympathetic paths may result in a relative increase in sphincter tonus.

3. Increase in sphincter tonus may also be due to damage to the central inhibitory pathways. Such pathways descend to the third nerve nucleus from the cortex and diencephalon, while others ascend to the nucleus over a diffuse system of afferent fibers in the reticular formation of the brain stem. Damage to them causes miosis by releasing the sphincter nucleus from inhibitory control.

4. A lesion in the light reflex pathway may lead to supersensitivity of the structures peripheral to the lesion (third nerve nucleus, ciliary ganglion, or sphincter muscle of the pupil). Hypersensitivity of denervated structures is well known both for adrenergic and for cholinergic mechanisms. The pertinent literature on this subject was summarized by Cannon and Rosenblueth.[7]

As an example, the dilator muscle of the iris becomes, some time after sympathetic denervation, hypersensitive to epinephrine, among other substances. When the blood epinephrine level rises under the influence of physical or emotional stress, the pupil on the denervated side dilates, and may become even larger than the normal pupil. Similarly, the cholinergic sphincter muscle, the ciliary ganglion, or the third nerve nucleus may become hypersensitive to acetylcholine when the structure has been deprived of its central connections, thus giving rise to miosis.

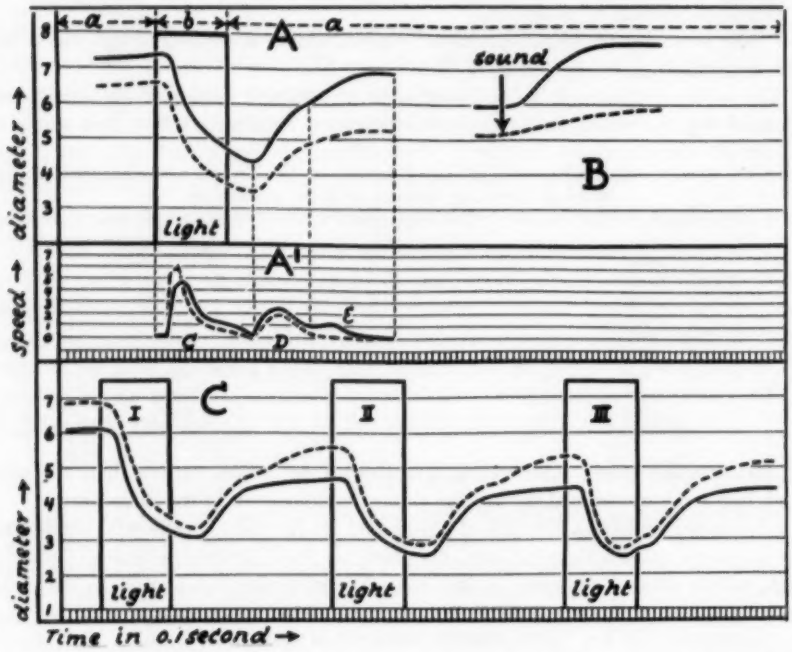

Fig. 1.—Reactions to light and to sound stimuli in two cases with lesions in the peripheral sympathetic pathways.

In the pupillograms (A,B,C,) pupillary diameter is plotted (in millimeters) against time (in 0.1 second), whereby the solid line represents the right, the broken line the left, pupil. The differential curve A' shows the speed (in millimeters per second) at which pupillary contraction and dilation occur within the light reflex A. The differential curve is derived from the original pupillogram by plotting against time (in 0.1 second) the extent of motion (in 0.1 mm.) that occurs within each successive 0.1 second.

First line (A,A', and B): Case of a 5-year-old girl with left-sided preganglionic Horner's syndrome. In darkness (a), the pupil on the side of the injury is slightly smaller than the normal pupil; its contraction to light (b) occurs slightly faster and earlier than that of the normal pupil (c-wave of differential curve A'), and its second redilation phase (e-wave of differential curve A') is almost absent. The anisocoria, therefore, is enhanced during the second redilation phase of the light reflex, as well as in the psychosensory dilation elicited by a sudden sound stimulus (B, indicated by arrow).

Second line (C): Case of a 47-year-old woman with right-sided (preganglionic) Horner's syndrome. The first, second, and third reactions of a continuous series of light reflexes are shown. The anisocoria, which amounts to 0.9 mm. in darkness, tends to disappear during the contractions to light and reappears during the second redilation phase of each light reflex (cf. III (A) of text).

To determine which of these mechanisms is responsible for the miosis appearing in the Argyll Robertson and related syndromes, the pupillary abnormalities caused by sympathetic lesions, by parasympathetic disinhibition, and by parasympathetic spasm must be known.

A. Effect of Sympathetic Lesions on Pupillary Size and Activity.—When the peripheral sympathetic path is interrupted, as clinically in Horner's syndrome or experimentally in animals, the pupil on the injured side becomes smaller than its fellow pupil. The resulting anisocoria is mild, the difference between the diameters of the two pupils seldom exceeding 2 mm. in man. The anisocoria is greatest in darkness and tends to diminish, or even to disappear, during repeated contractions to light (Fig. 1, *C*). It is increased during the second phase of redilation of the light reflex (Fig. 1, *A*) and is enhanced by sensory or emotional stimuli (Fig. 1, *B*). Since the sympathectomized pupil is smaller than the normal one, its

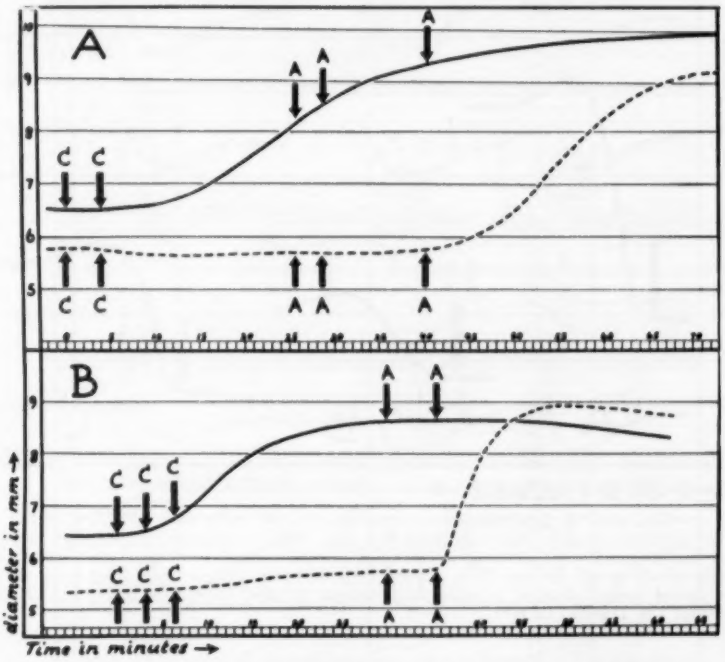

Fig. 2.—Effect of cocaine and epinephrine in cases with lesions in the peripheral sympathetic pathways.

Pupillary diameter is plotted as the ordinate (in millimeters) against time as the abscissa (in minutes); the solid line represents the normal pupil; the broken line, the pupil on the side of the lesion. Each of the arrows *C* indicates the time of instillation of 1 drop of cocaine hydrochloride (2%) into the right and left conjunctival sacs; each of the arrows *A*, the time of instillation of 1 drop of epinephrine hydrochloride (1 : 1000).

First line (*A*): Case of 54-year-old man with injury to the right (postganglionic) sympathetic fibers. The right pupil is about 1 mm. smaller than the normal, left one. Under the influence of cocaine the normal pupil dilates; the pupil on the side of the lesion remains unaffected. After additional instillation of 3 drops of epinephrine the pupil on the side of the lesion dilates and becomes almost as large as the normal pupil.

Second line (*B*): Case of a 57-year-old man, four months after surgical removal of the left superior cervical ganglion because of a ganglioneuroma. The pupillary dilator muscle has become hypersensitive to epinephrine. The pupil on the side of the lesion fails to dilate to cocaine; but when 2 drops of epinephrine are additionally instilled into each conjunctival sac, it dilates so strongly that it becomes larger than the normal pupil ("paradoxical pupillary dilation") (cf. III (*A*) of text).

light reflexes are usually somewhat less extensive than those on the normal side; but the contractions are always more forceful and, therefore, more rapid than normal. When the curve of speed variations is examined (differential curve, Fig. 1, *A'*), it becomes evident that the peak of contraction speed is higher and is reached earlier in the sympathectomized pupil.

When cocaine hydrochloride (2%) is instilled into the conjunctival sac of each eye, the normal pupil dilates but the sympathectomized pupil fails to respond. After additional instillation of epinephrine hydrochloride (1:1000), the normal pupil shows no further change, while the sympathectomized pupil dilates. If the lesion is preganglionic in respect to the superior cervical ganglion, or if only a part of the postganglionic fibers are interrupted, the sympathectomized pupil becomes as large, or almost as large, as the normal one. In complete postganglionic lesions in which hypersensitivity to epinephrine has developed, it may become even larger ("paradoxical pupillary dilatation," Fig. 2, *B*).

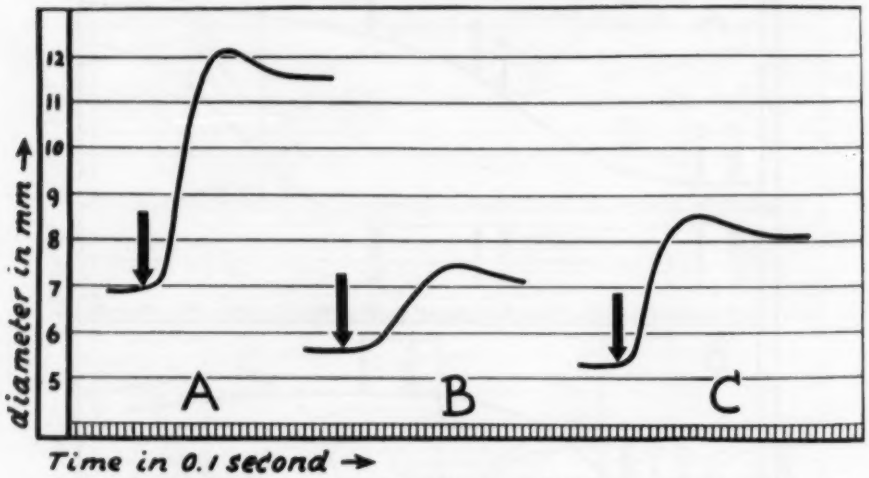

Fig. 3.—Reactions to psychosensory stimulation in cat (*A*), man (*B*), and monkey (*C*). Under identical experimental conditions, the cat's pupils are usually somewhat larger than those of man or monkeys. Under the influence of a sudden sound stimulus (indicated by arrows) the pupils dilate in all species. The dilation is greatest in the cat and smallest in man. The latency period before dilation is appreciably longer in man (0.3-0.5 second) than in animals (0.2 second) (cf. III (*A*) of text).

In our experience, clinical cases with damage to the cervical sympathetic chain show less hypersensitivity to epinephrine than is seen in experimental animals. When a superior cervical ganglion is removed from a cat or monkey, paradoxical pupillary dilation can easily be evoked by relatively mild psychosensory stimuli. In patients with a clinical Horner syndrome, we have not seen paradoxical dilation except after instillation of epinephrine into the conjunctival sac. This difference in sensitivity of man as compared with animals may arise from two facts: (1) Clinical lesions rarely are as complete as experimental removal of the superior cervical ganglion; (2) psychosensory dilation is not nearly as extensive in man as in monkeys and cats (Fig. 3).

When a parasympathicolytic drug, such as atropine sulfate or homatropine hydrobromide, is instilled into the conjunctival sac of each eye, the sympathectomized pupil does not dilate more extensively than the normal one.

B. Effect of Lesions Anterior to Third Nerve Nucleus Which Interrupt Supranuclear Inhibitory Fibers from Posterior Diencephalon.—When the inhibitory pathways running from the posterior diencephalon to the third nerve nucleus are destroyed by a clinical lesion in man, or experimentally in monkeys, the pupils are bilaterally smaller than normal. After adaptation to darkness, their diameters range from 3.9 to 5.5 mm. Upon light stimulation, they contract more rapidly than normal after a slightly shorter-than-normal latency period. Full contraction is thereby reached earlier than in normal cases and is maintained until redilation occurs, some time after the end of the light stimulus. The characteristic square "tonohaptic" reflex shape is thereby produced. Psychosensory dilation is unimpaired in these cases if the lesion is confined to an area fairly close to the midline (Fig. 4).

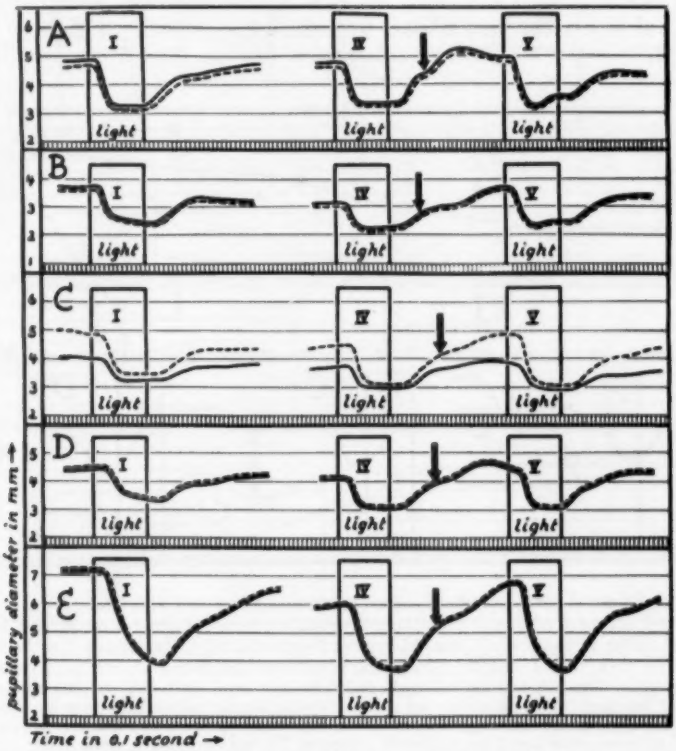

Fig. 4.—Effect of lesions anterior to the third nerve nucleus which interrupt supranuclear inhibitory fibers from cortex and diencephalon.

Pupillary diameter (in millimeters) is plotted against time (in 0.1 second), whereby the right pupil is represented by the solid line, the left pupil by the broken line.

Each line shows the first, fourth, and fifth reactions to light of a continuous series of reflexes. A psychosensory stimulus (sudden sound) is interposed between the fourth and the fifth light reflex of each series (indicated by arrows).

A: Experimental monkey (Macaca mulatta). A lesion had been produced anterior to the third nerve nucleus, extending about 1.5 mm. from the midline to each side.

B: Case of cerebral arteriosclerosis; 64-year-old woman with spastic deep reflexes in both lower extremities, essential hypertension, and emotional imbalance.

C: Case of essential narcolepsy; 24-year-old man with sudden overwhelming paroxysms of sleep, loss of muscle tone under influence of emotions.

D: Case of choreoathetosis after infection of unknown nature in a 20-year-old youth.

E: Normal pupillogram (for comparison).

In *A-D*, "tonohaptic" reflex shapes occur throughout; they are not reintegrated by the psychosensory stimulus, in spite of good psychosensory dilatation.

When cocaine hydrochloride (2%) is instilled into the conjunctival sac, the pupils dilate normally, and they contract well to parasympatheticomimetic drugs. The dilation to parasympathicolytic drugs is somewhat more extensive than in normal dark-adapted eyes.

C. Effect of Parasympathetic Spasm on Pupillary Size and Activity.—The effect of parasympathetic spasm may be studied pharmacodynamically. Any degree of spasm can be produced at will by drugs such as physostigmine salicylate or isoflurophate (D. F. P.) as is illustrated by the experiments of Figure 5: One drop of a 1% solution of physostigmine salicylate was instilled into the left conjunctival sac of a normal subject. The pupil contracted to 2.75 mm. within 31 minutes. Pupillary reactions to light were recorded before application of the drug and at various levels of drug action (Fig. 5, *B, C, D*). The light stimuli lasted one second and had an intensity of 16 f-c. The light reflexes were elicited by stimulation of the nontreated, right eye, whereby the pupil of the treated, left eye reacted consensually. With

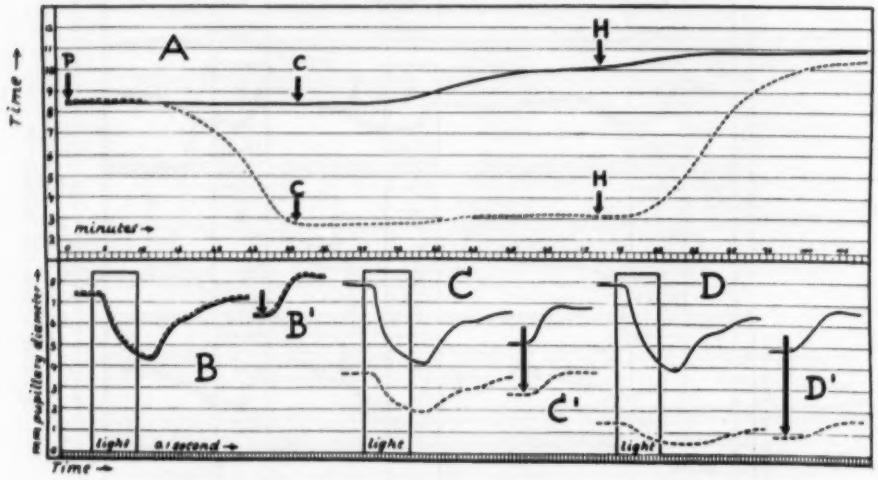

Fig. 5.—Effect of parasympathetic spasm on pupillary size and activity.

Pupillary diameter is plotted (in millimeters) against time (in minutes in the first line and in 0.1 second in the second line). The solid line represents the right, the broken line the left, pupil.

First line (*A*): The arrow *P* indicates the moment of instillation of 1 drop of physostigmine salicylate (1%) into the left conjunctival sac. The left pupil contracts to 2.75 mm. within 31 minutes. After instillation of 1 drop of cocaine hydrochloride (2%) into each conjunctival sac (arrows *C*), the right pupil dilates from 8.4 to 10.3 mm.; the left pupil, from 2.75 to 3.2 mm. within 45 minutes. Additional instillation of 1 drop of 1% homatropine hydrobromide (arrows *H*) causes little further dilation of the almost maximally dilated right pupil, but extensive dilation of the previously physostigminized left pupil (to 10.4 mm. within 35 minutes).

Second line: Light reflexes (*B,C,D*) and responses to psychosensory stimuli (*B',C',D'*) were elicited before instillation of drugs (*B* and *B'*), as well as 25 minutes (*C* and *C'*) and 30 minutes (*D* and *D'*) after instillation of physostigmine into the left conjunctival sac. As the physostigmine miosis progresses, the reactions to light become sluggish and less extensive and show delayed redilation. Reflex dilation to psychosensory stimuli is not abolished but reduced when compared with the simultaneous reactions of the nontreated pupil.

increasing miosis, the reactions to light became less extensive and increasingly sluggish. At fully developed physostigmine contraction, the remnant light reflexes showed an increased latency period, sluggish contraction, and delayed redilation. Reflex dilation to psychosensory stimuli was reduced but not abolished (Fig. 5, *B',C',D'*). When 2 drops of cocaine hydrochloride (2%) were instilled into each

conjunctival sac, both pupils dilated; the nonphysostigminized, right pupil reached a diameter of 10.3 mm., and the previously physostigminized, left pupil dilated to 3.2 mm. within 43 minutes. At this time, 1 drop of homatropine hydrobromide (1%) was instilled into each conjunctival sac. While the right pupil, owing to its almost maximal diameter, showed very little further dilation, the physostigminized, left pupil dilated extensively and became almost as large as the right pupil.

IV. MIOSIS IN CLINICAL CASES OF ARGYLL ROBERTSON AND RELATED SYNDROMES

Since, as was seen above, pupillary size and behavior in cases of miosis due to abnormal parasympathetic activity, to peripheral sympathetic lesions, and to damage

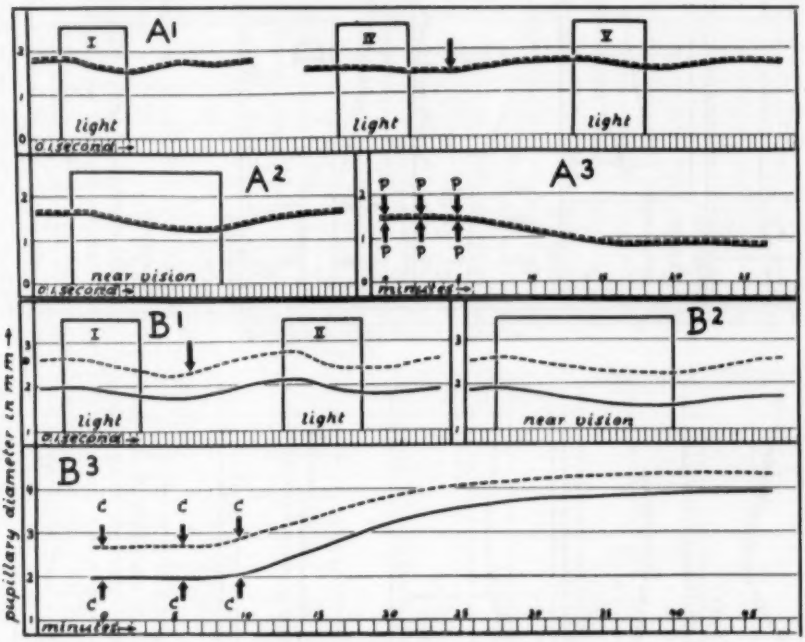

Fig. 6.—Pupillograms of two cases of tabes dorsalis in which reactions to light and to near vision are equally poor ("absolute pupillary immobility").

In these and in all following cases, the solid line represents the right pupil; the broken line, the left pupil. Pupillary diameter is plotted as the ordinate (in millimeters) against time as the abscissa (in 0.1 second for pupillary reflexes and in minutes for the reactions to drugs).

Case 1: (*A*): Both pupils are miotic (1.8 mm.). Only traces of the reflexes to light and to psychosensory stimuli (sudden sound, indicated by arrow in A^1) are visible; the contraction to near vision is equally poor (A^2). Instillation of 3 drops of physostigmine salicylate (2%) into each conjunctival sac (arrows *P* of A^3) causes further constriction to a mechanical minimum of 0.9 mm. within 17 minutes.

Case 2 (*B*): Both pupils are miotic, with the right pupil (diameter 2 mm.) smaller than the left (diameter 2.6 mm.). All reflexes are greatly diminished (B^1,B^2). Dilation after instillation of 3 drops of cocaine hydrochloride (2% indicated by arrows *C* in B^3) is relatively extensive about 2 mm. in 45 minutes).

in the central inhibitory pathways differ clearly from one another, it is possible to determine the cause of miosis in any given clinical case.

Figures 6 to 10 show pupillograms of eight representative clinical cases of the Argyll Robertson syndrome or "absolute" pupillary immobility with miosis. They were chosen from a group of 126 similar cases available in this laboratory. Of these

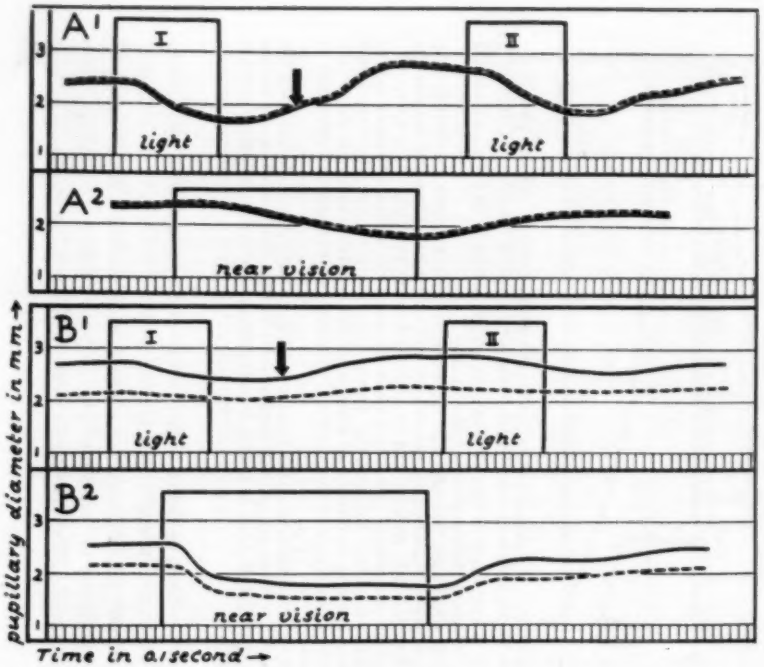

Fig. 7.—Pupillograms of two cases of syphilis of the central nervous system.

Case *A*: Miotic pupils with incomplete "absolute" pupillary immobility. The remnant reflexes to light are sluggish and inextensive, with prolonged latency period for contraction and delayed redilation. Reflex dilation in response to a sudden sound stimulus (arrow), as well as the second redilation phase of the light reflex are relatively well preserved (A^1). The reaction to near vision is at least as poor as the reactions to light (A^2).

Case *B*: Argyll Robertson syndrome. The reactions to light are almost absent, and the reaction to psychosensory stimulation is greatly reduced (B^1). In contrast, the reaction to near vision is prompt and relatively extensive (B^2).

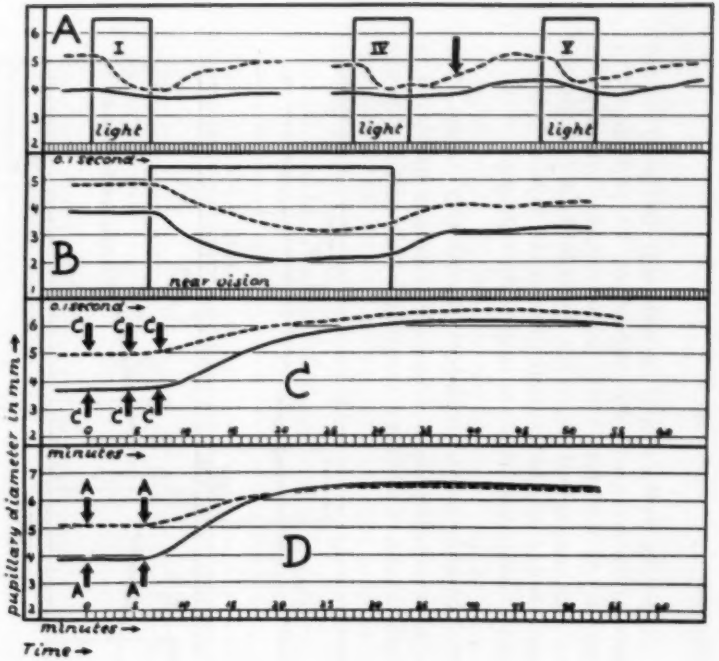

Fig. 8.—Argyll Robertson syndrome in a case of syphilis of the central nervous system.

A: The reactions to light of the miotic, right pupil are almost absent; those of the nonmiotic, left pupil are poor. Psychosensory dilation of the miotic pupil in response to a sudden sound stimulus (arrow) is reduced but not abolished.

B: Both pupils contract promptly and fairly extensively to near vision.

C: Both pupils dilate to cocaine hydrochloride (2%), indicated by arrows *C*.

D: Both pupils dilate vigorously to homatropine hydrobromide (1%), indicated by arrows *A*.

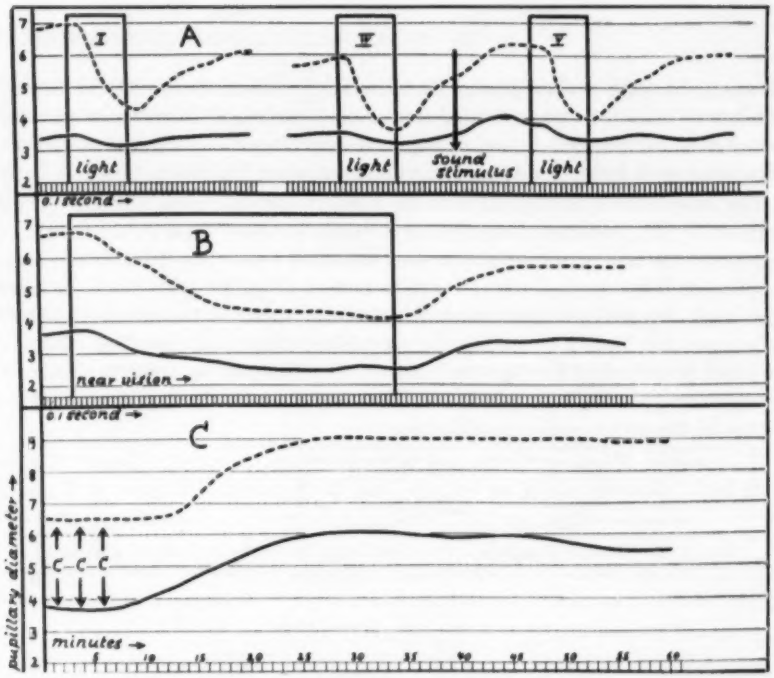

Fig. 9.—Unilateral Argyll Robertson syndrome in a case of syphilis of the central nervous system.

The responses of the left pupil are normal.

A: The reactions to light of the right pupil are inextensive and sluggish, while dilation in response to a psychosensory stimulus is relatively well preserved.

B: The contraction to near vision is more extensive than the reactions to light. The right pupil reaches a diameter of 2.5 mm. during the reaction to near vision, but becomes no smaller than 3.2 mm. in response to the light stimuli.

C: The dilation of the miotic pupil after instillation of 3 drops of cocaine hydrochloride (2%), indicated by arrows *C*, is as extensive as that of the normal side.

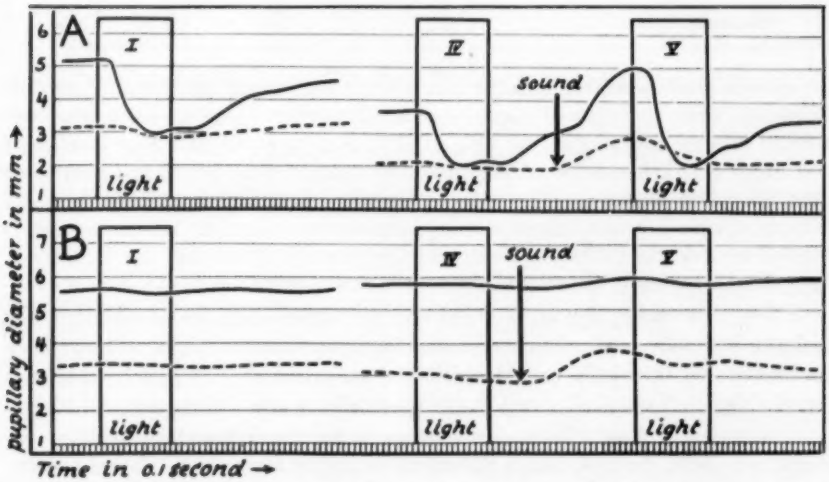

Fig. 10.—Miosis in a case of virus infection (*A*) and in a case of arteriosclerosis (*B*) of the central nervous system.

A: While the right pupil reacts fairly extensively to light, the contractions of the miotic, left pupil are minimal and very sluggish. Both pupils dilate well in response to a sudden sound stimulus, the right pupil more than the left one.

B: Both pupils are immobile to light, but only the left pupil is miotic. Under the influence of a sudden sound stimulus, the miotic, left pupil dilates more extensively than the nonmiotic, right pupil.

126 cases, 33 were unilateral and 93 bilateral. In 10 of the unilateral and 29 of the bilateral cases the uncomplicated syndrome occurred, while in the remaining 87 cases it was complicated by other pupillary pathology. The clinical conditions in which the Argyll Robertson or related syndromes were found are shown in Table 2.

The cases shown in Figures 6 to 10 were as follows: tabes dorsalis (Figs. 6, *A* and *B*; 7, *B*), syphilis of the central nervous system (Figs. 7, *A*; 8; 9), virus infection of the central nervous system of unknown type (Fig. 10, *A*), and arteriosclerotic condition of the central nervous system (Fig. 10, *B*). Since the present paper deals only with the mechanism directly responsible for the miosis, descriptions of the cases are limited to stating the established diagnoses. Detailed clinical histories and neurological findings are omitted. The illustrations serve to demonstrate the pupillographic findings, which are, more or less fully developed, present in all patients of the group under consideration.

1. *Degree of Miosis.*—Miosis may be extreme. In the case of Figure 6, *A*, both pupils had a diameter of 1.7 to 1.8 mm., and in the cases of Figures 6, *B* and 7, *B*

TABLE 2.—*Clinical Conditions Associated with Miosis in the Argyll Robertson or Related Syndromes*

	Type of Miosis					
	Unilateral		Bilateral			
Disease	Uncomplicated	Complicated	Uncomplicated	Complicated	Total	Percentage
Tabes dorsalis	3	2	8	16		
Cerebral syphilis	3	4	9	15	65	51.6
Dementia paralytica	..	1	..	4		
Multiple sclerosis	1	2	3	7	13	10.3
Virus infection	2	5	1	4	12	9.5
Heredodegenerative condition	1	3	2	4	10	7.9
Arteriosclerosis cerebri	..	1	5	7	13	10.3
Posteoncussion syndrome	..	3	..	1	4	3.2
Other conditions	..	2	1	6	9	7.2
Totals	10	23	29	64	126	
	33		93			
Percentage	26.2		73.8			100

the smaller pupil measured about 2 mm. This is not yet the mechanically possible minimum, since these small pupils contracted further when physostigmine was instilled into the conjunctival sac (Fig. 6, A^3). Seventeen minutes after instillation of 3 drops of a 2% solution of physostigmine salicylate, the pupils had contracted from the initial diameter of 1.6 mm. to slightly less than 1 mm. Such cases of extreme miosis are less common than is generally assumed. When the eye is adapted to darkness and accommodation-convergence is prevented, the majority of cases show a pupillary diameter slightly more than 3 mm.

2. *The Remnant Reflex to Light.*—Under the same experimental conditions the clinically immobile pupil often shows pupillographic traces of light reflexes. They are inextensive, invariably very sluggish, and are preceded by a prolonged latency period (Figs. 6, *A* and *B*; 7, *A* and *B*, and the smaller pupils of Figs. 8, 9, and 10, *A*).

3. *Reaction to Near Vision.*—In contrast to the sluggish and inextensive contractions to light, cases of Argyll Robertson syndrome often show relatively extensive and prompt contractions to near vision (Figs. 7, *B*; 8, and 9). In the "absolute" pupillary immobility syndrome, remnant contractions to near vision are as poor as, or even poorer than, the remnant reflexes to light (Figs. 6, *A* and *B*; 7, *A*).

4. *Reflex Dilations.*—Contrary to widely held opinion, reflex dilation in response to psychosensory stimuli is seldom abolished in cases of Argyll Robertson syndrome and "absolute" pupillary immobility with miosis. It is frequently quite extensive (Figs. 7, *A*; 9; 10, *A* and *B*), though usually reduced as compared with the normal pupil. Reduction of the reflex dilation in these cases is definitely not due to impairment of the sympathetic dilator path, as shown by the facts that (1) the second redilation phase of the remnant light reflexes is not abolished and (2) the pupil dilates well to cocaine (Figs. 6, *B*; 8, and 9). It should be recalled that reflex dilation of the normal physostigminized pupil is similarly reduced (cf. Figs. 5, *C'* and *D'*).

In clinical cases in which reflex dilation is absent, this may be due to two possible causes:

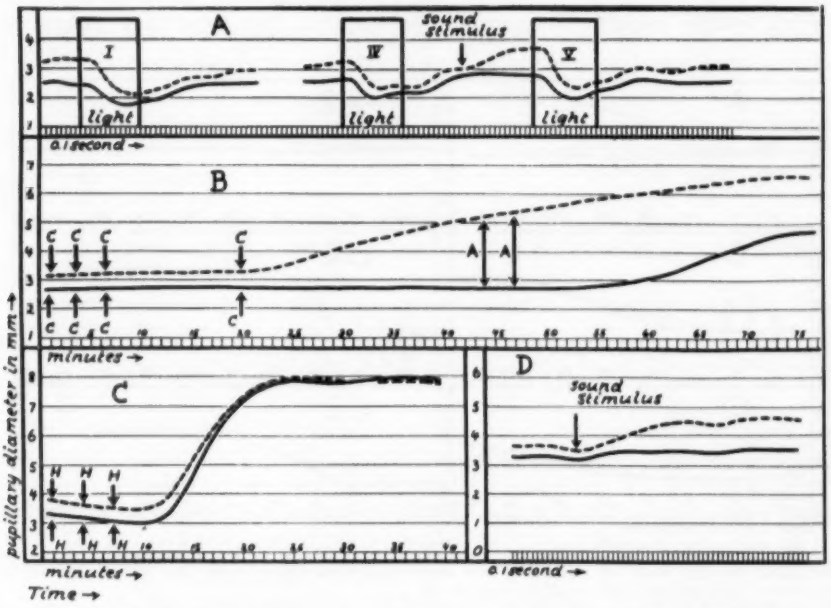

Fig. 11.—Bilateral miosis complicated by anisocoria due to damage to the peripheral sympathetic pathways on the right side.

A and *D*: In darkness, both pupils are miotic; the right pupil is up to 1 mm. smaller than the left pupil. This anisocoria tends to disappear during the inextensive and sluggish contractions to light and reappears during the second redilation phase of the light reflexes. It is enhanced by a psychosensory stimulus (sudden sound in *A* and *D*), which causes the left pupil to dilate more than the right one.

B: The smaller right pupil fails to dilate after instillation of 3 drops of cocaine hydrochloride into each conjunctival sac (arrows *C*) but does dilate when 2 drops of a 1:1000 solution of epinephrine hydrochloride are additionally instilled into each eye (arrows *A*).

C: Both pupils dilate extensively when homatropine hydrobromide (2%, arrows *H*) is instilled, reaching a diameter of almost 8 mm.

(*a*) Iris damage or synechiae. In such cases the pupil fails to respond to all physiological stimuli and reacts poorly even to drugs.

(*b*) Independent additional damage to the sympathetic pathways. Such additional sympathetic lesions are usually unilateral. They occur frequently in the general population, and there is no reason why they should not be found also in patients with the Argyll Robertson or related syndromes. Figure 11 demonstrates

a case of bilateral miosis with additional peripheral sympathetic damage on the right side. Both pupils are miotic, but the right pupil is even smaller than the left. The anisocoria (up to 1 mm. in darkness) tends to disappear during contraction to light. It increases during the second redilation phase of the remnant light reflex and after psychosensory stimuli. The diagnosis of superimposed sympathetic damage on the right side is confirmed by pharmacodynamic tests (Fig. 11, *B*). The right pupil fails to dilate to cocaine (2%) but does dilate when epinephrine hydrochloride (1:1000) is added.

5. *Effect of Parasympatheticolytic Drugs.*—When a parasympatheticolytic drug, such as atropine sulfate or homatropine hydrobromide (2%) is instilled into the conjunctival sac, the normal dark-adapted pupil dilates only slightly (Fig. 12, A^2). This can easily be understood because the iris sphincter of the normal pupil is already relaxed when the eye is adapted to darkness; the action of the drug, therefore, cannot become evident. The generally held opinion that these drugs dilate the

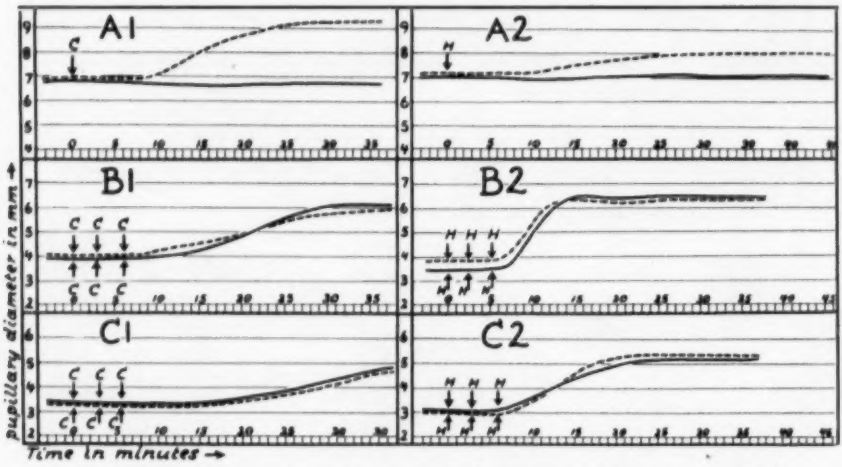

Fig. 12.—Effect of homatropine and of cocaine on the diameter of the normal pupil (*A*) and on the pupils in two cases of syphilis of the central nervous system with the Argyll Robertson syndrome (*B*) and absolute pupillary immobility (*C*).

First line (*A*): Both experiments were performed on the same normal human subject, with an interval of three weeks between experiments. The solid line represents the non-treated, right pupil; the broken line, the left pupil.

A^1: Instillation of 1 drop of cocaine hydrochloride (2%) into the left conjunctival sac. After 7 minutes, the left pupil begins to dilate and reaches a maximal diameter of 9.2 mm. after 28 minutes.

A^2: Instillation of 1 drop of homatropine hydrobromide (2%) into the left conjunctival sac. Ten minutes later, the left pupil begins to dilate; the dilation is less extensive and considerably slower than in Experiment A^1 and reaches a diameter of 8.1 mm. within 33 minutes. By this time, the reactions to light of the left pupil had been completely abolished, thus proving that the parasympathetic supply to the iris was completely paralyzed.

Second line (*B*): Bilateral Argyll Robertson pupil.

B^1: Instillation of 3 drops of cocaine hydrochloride (2%) into each conjunctival sac. The pupils dilate from an initial diameter of 4 mm. to one of 6 mm. within 35 minutes.

B^2: Instillation of an equal amount of homatropine hydrobromide. The pupils dilate to 6.5 mm. within 16 minutes.

Third line (*C*): Case with "absolute" pupillary immobility on both sides.

C^1: Instillation of 3 drops of cocaine hydrochloride (2%). The miotic pupils dilate slowly and inextensively to 4.7 mm. within 45 minutes.

C^2: Instillation of homatropine hydrobromide (2%). The pupils dilate to 5.3 mm. within 25 minutes.

In the two clinical cases, therefore, dilation to homatropine is more extensive and more vigorous than dilation to cocaine; this is the reverse of the normal findings.

normal pupil widely is based on the fact that most workers observe the drug reaction in light. Parasympatheticolytic drugs abolish the light reflex; this is why dilation under their influence seems greater when observed in light than when the test is performed in darkness.

In cases of miosis as a part of the Argyll Robertson and related syndromes, the pupil fails to dilate in darkness but dilates promptly when parasympatheticolytic drugs are instilled into the conjunctival sac (Figs. 8, *D*; 11, *C*; 12, B^2 and C^2). In some cases, the pupil reaches a diameter of 7-8 mm., i. e., normal size; in others, particularly in advanced cases with iris damage, it may not reach normal size. Generally the dilation curve is more extensive and prompter than that for the normal dark-adapted pupil (cf. *A* with *B* and *C*, Fig. 12).

SUMMARY AND CONCLUSIONS

Experimental and clinical pupillographic studies combined with pharmacodynamic tests established the following general rules for distinguishing the various types of miosis:

A. Cases of Miosis Due to Damage in the Sympathetic Pathways to the Dilator Muscle of the Iris.—1. Miosis is present to a mild degree. It is generally, but not necessarily, unilateral.

2. Contraction to light is slightly faster than normal.

3. The second redilation phase in the pupillographic picture of the reflex to light is absent.

4. Reflex dilation is sluggish; its extent is reduced to approximately one-fifth of the normal value.

5. The pupil fails to dilate after instillation of cocaine hydrochloride (2%) into the conjunctival sac.‡

6. The pupil dilates when epinephrine hydrochloride (1:1000) is instilled. In cases with preganglionic or with incomplete postganglionic sympathetic lesions it becomes approximately as large as the normal pupil. In complete postganglionic lesions, it may become even larger.

7. Dilation to homatropine hydrobromide (2%), when the test is performed in darkness, is normal or slightly reduced.

B. Cases with Damage of the Supranuclear Inhibition Pathways Running to the Edinger-Westphal Nucleus.—1. Miosis is always bilateral. The pupils are smaller than in the cases grouped under *A*. Their diameters range from 3 to 5 mm. (after adaptation to darkness).

2. Contraction to light is much faster than normal. The pupillary reflex to light shows the square-shaped, "tonohaptic" reaction pattern.

3. The second redilation phase of the pupillary reflex to light is preserved (in contrast to the type in *A*).

4. Reflex dilation in response to psychosensory stimuli is normal.

5. The pupils dilate normally after instillation of cocaine hydrochloride (2%) into the conjunctival sac.

6. They do not dilate after instillation of epinephrine hydrochloride (1:1000).

‡ It should be stressed that large amounts of cocaine (several drops of a 4% or 5% solution) will dilate the sympathectomized pupil by paralyzing the sphincter muscle. High concentrations of cocaine should, therefore, be avoided, in carrying out this test.

7. Dilation to homatropine hydrobromide (2%) is normal or increased.

C. Miosis Due to Parasympathetic Spasm.—1. Any degree of miosis may be found. It may be either unilateral or bilateral.

2. The reaction to light is sluggish and inextensive or absent.

3. The second redilation phase in the remnant light reflexes is preserved.

4. Dilation in response to psychosensory stimuli may be, but is not always, reduced.

5. The pupils dilate up to normal values to cocaine hydrochloride (2%).

6. They do not dilate to epinephrine hydrochloride (1:1000 solution).

7. Dilation to homatropine hydrobromide (2%) is prompt and extensive; it may reach up to five times the normal values.

It was shown that the miosis encountered in clinical cases with the Argyll Robertson and related syndromes, such as "absolute" pupillary immobility, shows all signs described under category *C*. The miosis in such cases, therefore, is due to parasympathetic spasm and not to absence of sympathetic innervation. It is cholinergic in nature, as proved by the prompt dilation to parasympatheticolytic drugs in cases in which the pupil fails to dilate in darkness.

We have refrained from discussing the possible processes responsible for the abnormal parasympathetic activity, i. e., whether it is due to hypersensitivity of a denervated sphincter muscle or to an irritated or supersensitive nervous structure controlling the muscle. This question, as well as the related question of the probable site of the lesion in the Argyll Robertson and related pupillary syndromes, will be the subject of a future publication.

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Critical Fusion Frequency in Retrobulbar Neuritis

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Poor vision and visual field changes, particularly a central scotoma, are characteristic features of most cases of retrobulbar neuritis. It is remarkable in this type of disease that no changes can be found ophthalmoscopically in the fundus, at least at the beginning stage of the disease.

In the present paper we shall report on the behavior of critical fusion frequency of flickering light (CFF) in patients with retrobulbar neuritis. Experiments were carried out with special reference to the CFF at the retinal region corresponding to the central scotoma.

There can be found only a few reports which are concerned with the CFF in retrobulbar neuritis.[1] In a number of cases of diseases of the optic nerve, some of which may belong to the type of retrobulbar neuritis, Braunstein,[2] Riddell,[3] Hylkema,* and others found that the CFF was decreased more or less at the area of deteriorated vision.

METHOD

In the present experiment, an intermittent light was provided by driving a neon-glow tube, with a suitable electric circuit.

The flash duration was fixed at 1.84 msec. throughout the present experiment. A large plate of mat glass at a distance of 50 cm. in front of the subject's eye was illuminated from behind by the intermittent light, and a small portion of the illuminated glass was used as a test target, its size being varied from 0.5 to 3.75 degrees. By means of a suitable lens the subject could see the target without any effort of accommodation. The light intensity of the stimulus target ranged from 0.17 to 2.28 millilamberts (mL).

The determination of CFF was carried out in the following way: At first the intermittent light of sufficiently low frequency was presented to the subject for two seconds. Then the exposure was repeated, increasing the frequency of flashes step by step. Thus, the lowest frequency at which the subject had no sensation of flicker was determined as representing CFF. To secure reliability of the measurements, five readings of CFF were taken under one and the same experimental condition, and the obtained figures were averaged. The values of CFF presented in the following sections refer only to such averaged values.

RESULTS

CFF as a Function of Area of Stimulus Target

It is well known that CFF is increased in a logarithmic manner with increases in the area of the stimulus target (Granit-Harper law †). In our preliminary

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* References 4 and 5.

† References 6 and 7.

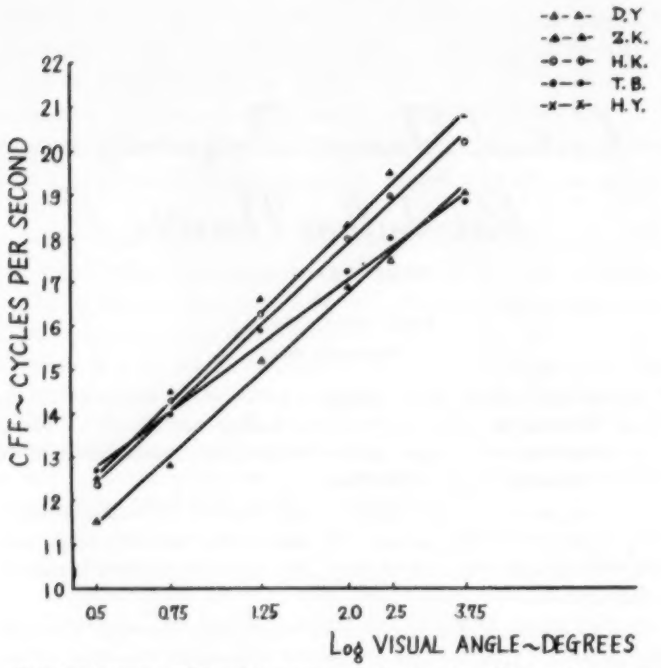

Fig. 1.—Relation between CFF and logarithm of stimulus area. Data of four normal subjects are demonstrated. Size of area is expressed in degrees of visual angle. Intensity of stimulus 2.28 mL.

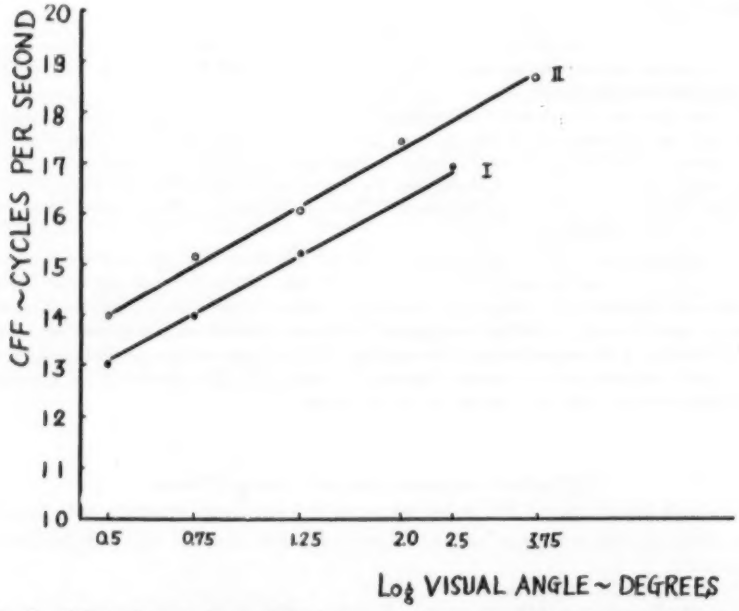

Fig. 2.—Effect of pupil size on CFF in normal subject. *I*, relation determined with natural pupil whose diameter was 4.0 mm.; *II*, relation determined with dilated pupil whose diameter was 7.5 mm.

experiment, we investigated whether the said relation holds under our experimental conditions. For this purpose four subjects who had no eye complaints and showed no pathological signs were randomly selected, and in these normal subjects the CFF was measured at visual angles varying from 0.5 to 3.75 degrees, the stimulus intensity being fixed at 2.28 mL.

Data obtained from these subjects are represented in Figure 1, in which the CFF's are plotted against the logarithm of the stimulus intensity, as abscissa. As will be seen from this Figure, under our experimental conditions the Granit-Harper law holds good in normal subjects; i. e., the CFF-log area relation is presented by a single straight line. It is also to be noted in Figure 1 that the slopes of the CFF-log area lines do not differ from one another to any considerable degree.

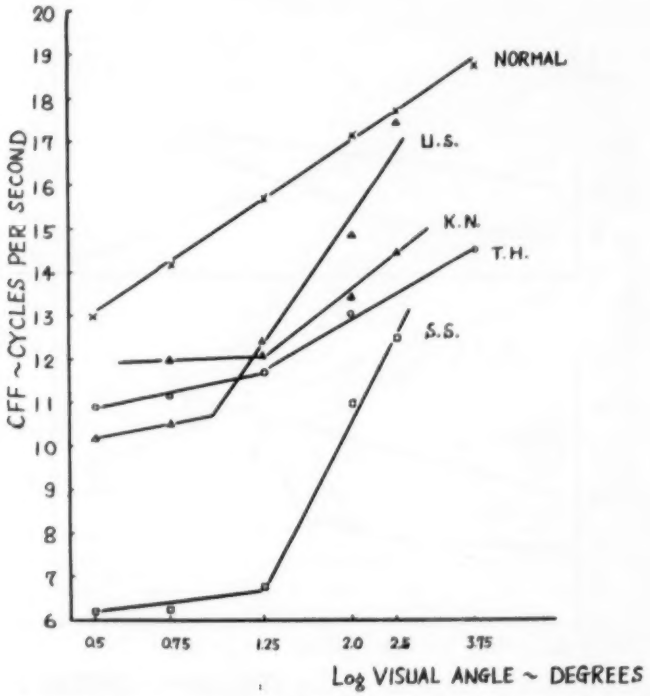

Fig. 3.—Relation between logarithm of size of stimulus area and CFF in retrobulbar neuritis with a central scotoma. Relation represented by crosses of a normal control. Intensity of stimulus 2.28 mL.

In the experiment mentioned above, no attention was paid to the fluctuation of the pupil size, which may occur in response to sudden exposure to light. In order to get information about the possible effect of the pupil size upon the relation between the CFF and the stimulus area, values of CFF's before and after instillation of homatropine hydrobromide were compared (Fig. 2). Homatropine, which caused the pupillary dilation and stopped the irregular movement of the pupil, was found to be effective in raising the CFF at all the visual angles used. However, it deserves attention that after the application of homatropine the slope of the CFF-log area relation was almost the same as before (Fig. 2). In other words, it seems likely that the slope of the CFF-log area line is not affected by the pupillary fluctuation.

In the measurements of CFF in patients with retrobulbar neuritis, the pupils were not treated with homatropine. But, on the basis of the above-mentioned control experiments in normal subjects, there seems to be no need to give any serious consideration to the effect of pupillary fluctuation upon the CFF so far as its relation to the stimulus area is concerned.

CFF-Log Area Relation in Patients

The method of measuring CFF at varying angles of the test target was applied to four cases of retrobulbar neuritis. Two of them were of the acute type and two of the chronic type. Their symptoms were as follows: Visual acuity was markedly reduced to a range from 0.2 to 0.05. A relative scotoma, which could be detected

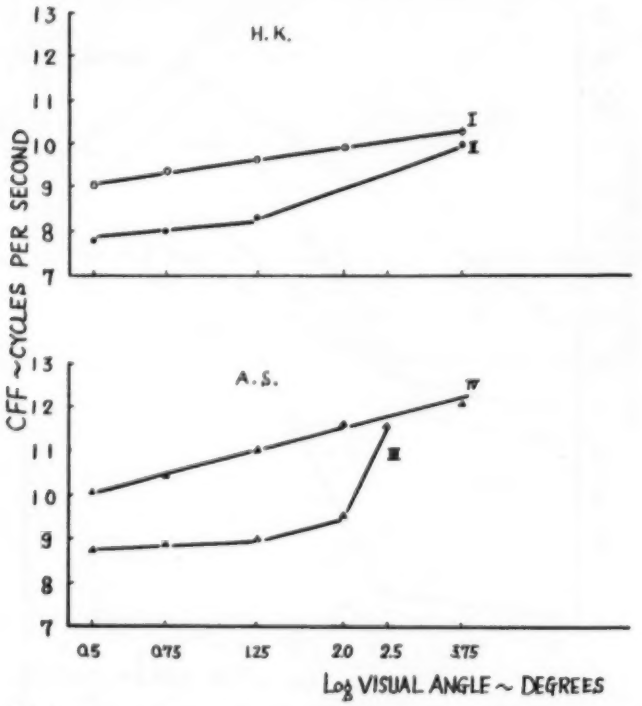

Fig. 4.—Relation between central scotoma and CFF-log area relation. Upper set: Patient H. K., Curve *II*: A central scotoma was found. Curve *I* (20 days later): No scotoma detected; Lower set: Patient A. S.: Curve *III*: A central scotoma was detected. Curve *IV* (20 days later): No scotoma detected.

in the central area of the visual field by the usual method of campimetry, varied from case to case with respect to its form and extent, but it was a feature common to all cases that the central region of the retina about 5 degrees in diameter was severely affected and appeared to be profoundly deteriorated with respect to color vision. Data obtained from these patients (U. S., K. N., T. H., S. S.) are presented in Figure 3, in which the curve for a normal control is also shown. As can be seen from this Figure, the CFF's for these patients were reduced at all the visual angles of the test target used. The reduction is very marked for Subject S. S., whose visual acuity is as poor as 0.05. Another remarkable feature to be seen from Figure 3 is

that the CFF-log area relation generally consists of two portions, one running nearly horizontally and the other having a slope of considerable magnitude.

It is difficult to attribute such findings to mere chance, for we can demonstrate two other cases in which similar reduction of CFF associated with a bending of the CFF-log area relation appeared or disappeared according to the status of the disease during our observation period. In Patient H. K. the CFF-log area relation was a straight line at the stage at which he began to complain of symptoms of retrobulbar neuritis without showing any distinct scotoma (curve *I*, Fig. 4). Twenty days later the relative central scotoma became easily detectable in his affected eye. At this time the CFF values at all visual angles were reduced as compared with those obtained at the initial examination. In addition, it became apparent that the

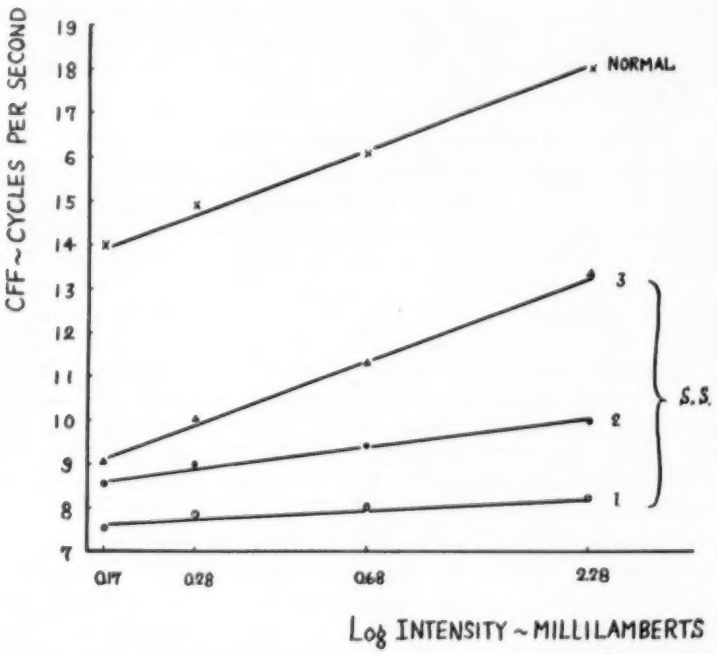

Fig. 5.—Relation between logarithm of stimulus intensity and CFF in retrobulbar neuritis. Relation represented by crosses was obtained from a normal subject. Size of stimulus area, 2.0 degrees in visual angle. Line *1*, at first; line *2*, 12 days later; line *3*, 33 days later.

CFF-curve was bent upward at the visual angle of about 1.25 degrees as the area of the target was increased (curve *II*, Fig. 4). A similar situation is seen in Patient A. S., also presented in Figure 4 (curves *III* and *IV*). The CFF-log area relation in Patient A. S. was found concave upward at the first examination, in which campimetry revealed a relative central scotoma in his affected eye, his visual acuity being 0.02. Twenty days later the CFF was redetermined and found to be increased at all the visual angles of the test target, and the CFF-log area relation was represented by a straight line. Such a change in the CFF-log area relation was accompanied by an improvement in symptoms; his visual acuity had increased to 0.2; the scotoma had almost disappeared, and color perception appeared to be improved.

In the preceding section we have pointed out that the CFF-log area relation consisted of two portions, one of them running almost parallel to the abscissa and the other having a steeper slope. Our tentative explanation for this feature is as follows: It can be considered that the central region of the retina has a function so much depressed that fusion takes place at a very low frequency in this region, and that this area is almost devoid of the capacity to increase the CFF in response to an increase in stimulus area. When a test target is so small in size that it is completely included in the area of the central scotoma, the CFF is reduced and is not increased until the test target exceeds the involved area. Under this condition, the CFF, plotted against the logarithms of the stimulus area, runs almost horizontal and is lower than those obtained in normal subjects. When the less deteriorated area surrounding the central scotoma is involved in the determination of CFF, this value increases with the stimulus area, so that the second portion, with a steeper slope of the curve, is produced. The critical size of test target at which the CFF began to increase in response to the increase in stimulus area was a diameter of about 1.25 degrees in our subjects.

CFF as a Function of Logarithm of Stimulus Intensity

We shall present additional evidence obtained from a patient with retrobulbar neuritis concerning CFF in relation to stimulus intensity (Fig. 5). In this case the CFF was measured at stimulus intensities varying from 0.17 to 2.28 mL, whereby the size of the test target was fixed at 2 degrees in visual angle. The lines *1*, *2*, and *3*, representing the CFF as a function of log intensity, were obtained in that order at successive stages at which the symptoms of the disease became progressively less severe. At each stage a fairly good linear relation was found to hold between the logarithm of intensity and the CFF. In addition to this, as the visual function of the patient progressively improved, the line of CFF-log intensity relation became progressively steeper. At the final stage the CFF-log intensity relation (line *3* in Figure 5) had almost the same slope as that obtained from a normal subject (cf. normal control in Fig. 5), though each value of the CFF in the patient was much reduced.

In the preceding section, we have suggested that the central retinal area with a depressed function had lost the capacity to increase the CFF in response to an increase in stimulus area. A similar situation can be seen from the data in Figure 5, in which the stimulus area was replaced by the stimulus intensity. Such a feature is conceivable when we consider that the area and intensity of the light stimulus, as a rule, can function interchangeably in respect to some kinds of retinal function; i. e., the effect of the increase in area at constant intensity is almost the same as that in the increase in intensity at the constant area.

COMMENT

Our data concerning the CFF in patients with retrobulbar neuritis show that the CFF in the region of the scotoma in the affected eye was greatly reduced and that the CFF-log area relation or the CFF-log intensity relation ran almost parallel to the abscissa within a certain range of area or intensity. Such a reduction in CFF as that found in our subjects might be ascribed to the condition that the stimulating light was absorbed more or less on its way through the ocular media to the photoreceptive layer of the retina. Such an interpretation, however, cannot be accepted. Miles [8] reported that CFF was not greatly changed in subjects who showed obvious defects in translucency of the ocular media, as revealed by ophthal-

moscopy. In our subjects the media were clear. Therefore we can safely exclude defects in translucency as the cause of the reduction in CFF in our patients.

Up to the present, it is widely accepted that the depressed vision in retrobulbar neuritis is caused by blocking of the nerve impulses in the retrobulbar optic nerve fibers, for the following reasons: 1. There are histopathological findings in severe cases of the disease, consisting of degenerative or of atrophic changes in the retrobulbar optic pathways. 2. It is our common experience that no changes can be observed in the fundus of the patients, at least at the beginning of the disease, though the patients complain of severe ocular symptoms. The symptoms of retrobulbar neuritis can be accounted for by a blocking of the impulses in the retrobulbar optic pathway.

We may, however, point out that there is another possibility concerning the site of affection. If the nerve impulses are not properly integrated before they reach the ganglionic layer in the retina, the same symptoms may occur as in the case of a block in the retrobulbar fibers. In other words, there is a possibility that the functional deterioration in the neuronal network of the bipolar cell layer may cause the symptoms of retrobulbar neuritis. This interpretation seems to conform well with our findings. In the first place, it will be recalled that all the patients examined by us had the following symptoms in common: Their visual acuity was profoundly reduced and their color vision was achromatic so far as the retinal area showing the scotoma is concerned. On the other hand, it is well known that rod-monochromatism, as the type of congenital achromatopsia, is characterized by reduced visual acuity, achromatic color vision, etc. Rod-monochromatism and retrobulbar neuritis are similar to each other with respect to these clinical symptoms.

Another functional similarity between the two cases can also be found in the behavior of CFF under varying conditions of stimulation. Ajo and Teräskeli [9] found in two rod-monochromats that the CFF was greatly reduced and that the increase in the stimulus area was ineffective in increasing the CFF. We could confirm the findings of the above-mentioned authors and extended our observations to the effect of stimulus intensity upon CFF. The subject who was examined by us was found to be a rod-monochromat of congenital type, because his visibility curve had its maximum at 510 mμ, irrespective of the state of adaptation of the eye, and visual acuity was profoundly reduced. In this subject CFF was measured in the same manner as in the patients with retrobulbar neuritis. As will be seen from Figure 6, the CFF was scarcely increased by the increase in stimulus area (upper set, Fig. 6) or by the increase in stimulus intensity (lower set). The behavior of the CFF is closely similar to that found in the patients with retrobulbar neuritis.

We may now consider the site of affection in the rod-monochromat. Two possibilities have been thought of: (1) a defect in color-receptive mechanism in the retina and (2) a defect in the central nervous pathway or in the central receiving center. Strictly speaking, we cannot say which theory is more probable, at least on the basis of our present knowledge.

Recently Motokawa [10] developed a new technique which has enabled us to analyze the visual function at the retinal level without taking the central receiving mechanism into consideration. With Motokawa's technique, Yonemura and Ishisaka [11] studied the retinal function in rod-monochromatism of congenital type and obtained evidence that the absence of color vision in the rod-monochromat is caused almost exclusively by the functional deterioration at the retinal level. In this respect, it is worth noting Polyak's opinion [12] that the color-discriminative

function can be executed by the neuronal network in the bipolar cell layer of the retina.

From these considerations we may reach the conclusion that the defect in the neuronal network of the bipolar cell layer is a cause of the symptoms which are characteristic of rod-monochromatism.

As the retrobulbar neuritis and the rod-monochromatism are closely similar to each other in clinical symptoms, such as depressed vision, as well as in the behavior of the CFF, we are led to the following consideration: If the functional disturbance occurs in the bipolar cell layer of the retina, there may appear the above-mentioned symptoms of retrobulbar neuritis. Thus, it seems unnecessary that

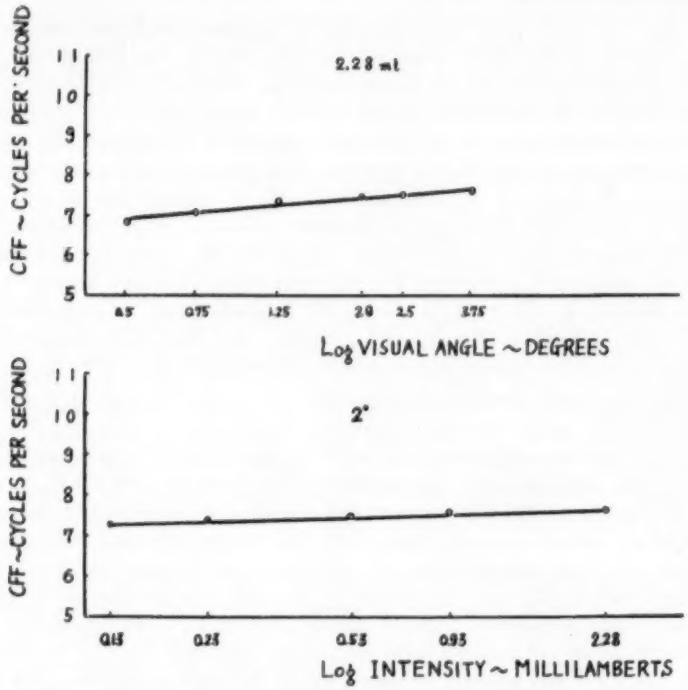

Fig. 6.—CFF in congenital achromatopsia. Upper set: CFF-log area relation. Intensity of stimulus 2.28 mL. Lower set: CFF-log intensity relation. Size of stimulus area, 2 degrees in visual angle.

these symptoms of the disease must be ascribed exclusively to a blocking of the impulses in the retrobulbar optic pathway.

SUMMARY

In patients with retrobulbar neuritis, CFF (critical fusion frequency of flickering light) was measured at the central region showing the severe scotoma. The results were as follows:

1. As the area of the stimulus target was increased, the CFF in the patients failed to increase within the central area showing the scotoma, so that the CFF-log area relation was found to consist of two portions, with different slopes. The relation, however, was represented by a single straight line in normal subjects.

2. A similar result was obtained concerning the effect of the increase in stimulus intensity upon the CFF. The CFF-log intensity relation ran almost parallel to the abscissa within a certain range of stimulus intensity, while the normal eye showed a considerable increase of CFF within the same range.

A close similarity is pointed out between congenital achromatopsia and retrobulbar neuritis in the behavior of the CFF, as well as visual acuity and color vision.

It is suggested that the site of the block in the nerve impulses in so-called "retrobulbar" neuritis may actually be in the neuronal network of the bipolar cell layer, and not in the nerve fibers behind the globe, as has generally been thought.

Prof. K. Motokawa gave valuable criticism, and Prof. K. Iwama offered helpful discussion of the problem.

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Ocular Axes and Meridians During Oblique Oculorotations

A Contribution to the Problem of So-Called False Torsion

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New York

Two rather unrelated circumstances turned my attention lately to the problem of the behavior of the vertical and horizontal ocular meridians during oblique oculorotations, the problem of so-called false torsion. Though seemingly of purely academic interest, it has never ceased to intrigue ophthalmologists, up to the present day.

In a recent study of the horopter, I found myself in agreement with the conclusions of Luneburg, according to which the horopter is a torus of a sort, a peculiarly curved plane, all points of which subtend a constant angle (γ) with the centers of rotation of the two eyes. Bifixating the center P_o of a given horopter torus (the midpoint of the horizontal Vieth-Müller circle), the eyes converge γ degrees and are in what might be called the primary position of convergence. However, not only this point, but each and every point P of the toric structure can be similarly bifixated while the eyes maintain this fixed angle (γ) of convergence. Thus, the movements necessary to achieve bifixation always are version movements. The eyes might have to execute a positive or negative elevation movement of some angular value ψ (if the new point of bifixation is higher or lower than P_o), or a right or left declension movement of some angular value ϕ (if the new point of bifixation is to the right or left of P_o), or, finally, some oblique movement (if the new point of bifixation is up and to the right, or up and to the left, etc., either from P_o itself or from some other point P, toward which the foveas had previously turned). How such versions are executed during convergence certainly is a problem worth studying.

The generally held belief that oblique ocular rotations occur with preference around axes in Listing's plane is, according to Duke-Elder, primarily justified by the economy of such rotations. It is the least needed expenditure of effort and the fastest possible attainment of goal which characterize ocular rotations executed around such axes. This, no question, holds true in the case of monocular rotations and the case of $\gamma=0$ (the case in which the lines of fixation are parallel), but it is obviously not true for the version movements of converging eyes just described. To give only one example: The pure elevation of gaze from the primary position of convergence needed for the bifixation of some point P straight above P_o in the same horopter torus will be accomplished with the greatest ease under an act of

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simple supraversion around axes which are perpendicular to the lines of gaze. In fact, except for the just-mentioned case of $\gamma=0$, it is impossible for the eyes to maintain convergence ***and*** achieve speed and the desired economy of effort at the same time if version movements are to be carried out around axes lying in Listing's plane.

Obviously, Luneburg's concept of the horopter casts some doubt upon the preeminence or even the most desirable quality of ocular rotations around axes in Listing's plane. But there is even more to this new concept. It was made clear to me by the mathematician Prof. A. Blank, of Knoxville, Tenn., that the anatomical vertical meridians of the two eyes, when at rest, cannot both be covered by individual points of Luneburg's horopter (except in the case of $\gamma=0$). Once it is assumed that a vertical line elevated upon the point of symmetrical bifixation is contained within the horopter (this vertical is part of the so-called longitudinal horopter of the classic authors) and that its images cover pairs of corresponding points within those anatomical retinal vertical meridians, then the sum of visible points characterized by a constant angle γ cannot actually constitute the horopter, at least as defined for eyes at rest. Obviously, Luneburg's horopter of constant convergence angle is not identical with the longitudinal horopter. And in the case that the latter is *the* horopter of corresponding points, the former might not even merit to be called a horopter. Of course, it is just as well possible, or at least thinkable, that the anatomical vertical retinal meridians are not the carriers of corresponding points.

Both these currents of thought make one thing evident. Luneburg's concept of the geometry of the horopter either will lead to a modification, even to the abandonment, of some of the inherited concepts of visual physiology and ocular motor mechanics, or will itself have to be modified or abandoned. In any event, Luneburg's work will have acted as a welcome ferment of clarification. In my essay, I could do no more than express some of the doubts which these studies have aroused in me, concerning both the significance of Listing's law and the existence of predetermined vertical (or horizontal) retinal meridians with their ineffaceable "local signs" of verticality (or horizontality) innate to them, and I have lately been engaged in devising some experiments which should lead toward confirming the validity of one or the other of these opposing conceptual structures.

While examining the pertinent literature, my attention was inadvertently turned toward this problem by still another, and a very sad, circumstance: Dr. Pascal, for quite different reasons, and for a number of years, had also been engaged in a study of the behavior of the ocular meridians during oblique oculorotations. Several of his last papers were dealing with these. He was in the midst of a controversy concerning one special aspect of oblique oculorotations which he hoped soon to resolve, but from which he was prevented by his untimely death. He had had a great amount of correspondence with experts in the field and was in the process of preparing an exhibit of models and calculations for the June, 1955, meeting of the American Medical Association in Atlantic City. With the assistance of Mrs. Charlotte Pascal and one of Dr. Pascal's young associates, Dr. Harris Ripps, I engaged in setting up the exhibit as well I could. The exhibit consisted in part of a repeated showing of the classic after-image experiments of Ruete, Donders, Helmholtz, Le Conte, etc., but was mainly centered around two models of movable globes, one supplied by Dr. J. V. D. Quereau, of Reading, Pa.; the other, a most ingenious one, especially prepared for Dr. Pascal's exhibit by his friends Dr. David Hale and Dr. P. J. Berggren, of New York (Fig. 1).

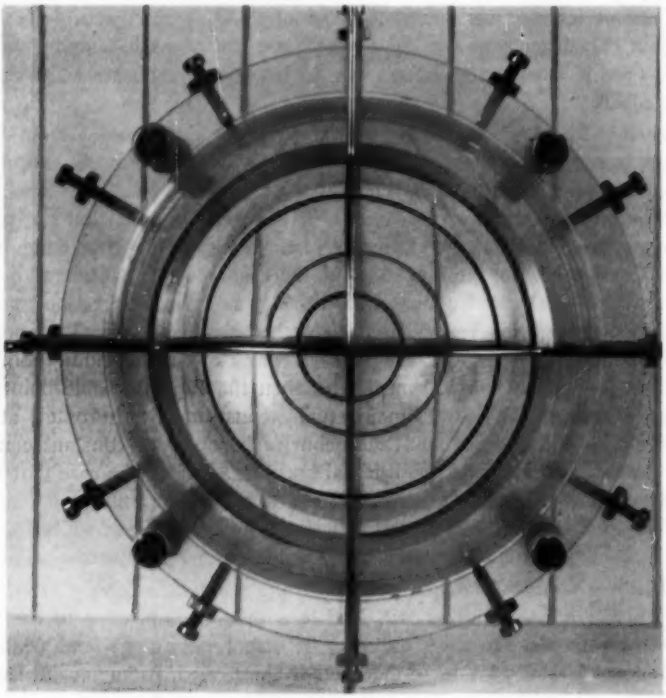

Fig. 1.—Pascal's model for the study of ocular rotations.

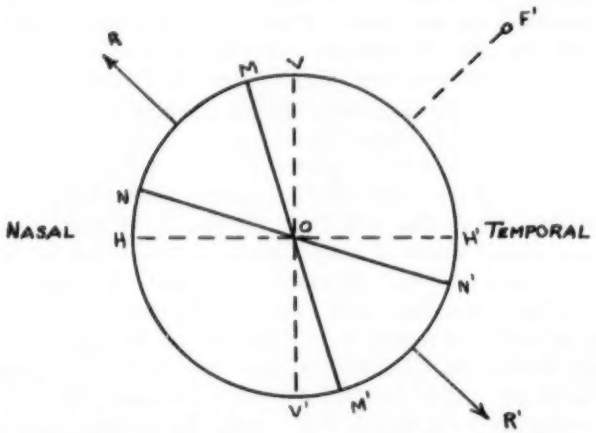

Fig. 2.—Apparent movement of the vertical and horizontal axes of the eye in opposite directions. Reproduced, with modifications and original legend, from Márquez, M.: Supposed Torsion of the Eye Around the Visual Axis in Oblique Directions of Gaze, Arch. Ophth. **41**:704, 1949, Fig. 6.

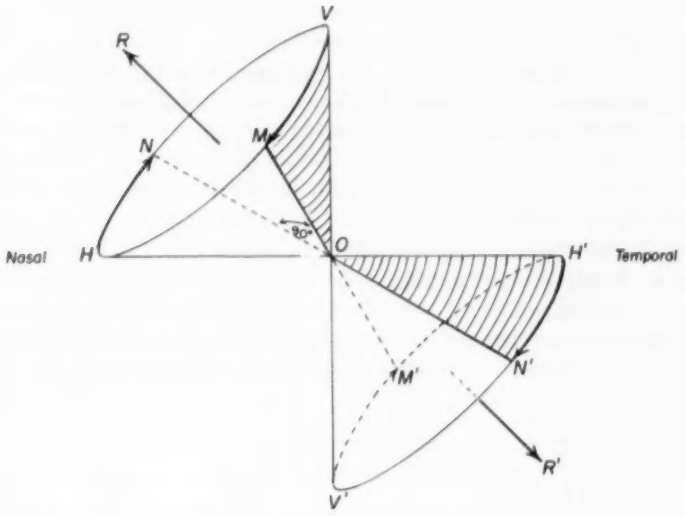

Fig. 3.—Perspective view of the displacement of the vertical and transverse axes as the eye rotates around the RR' axis in Listing's plane.

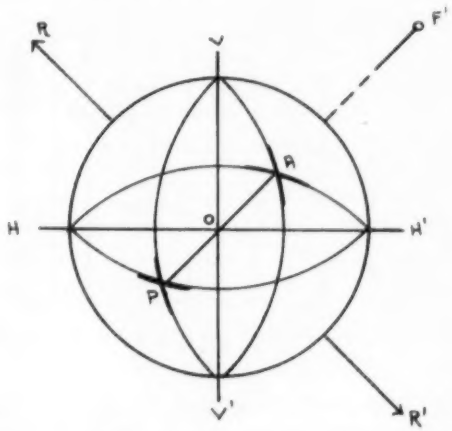

Fig. 4.—Axes of the eye and the vertical and horizontal meridians of the anterior segment (A) and the posterior segment (P). Reproduced, with modifications and original legend, from Márquez, M.: Arch. Ophth. **41**:704, 1949, Fig. 5.

It is hoped that the description of a few experiments carried out with these models will add to the settling of a controversy in which Dr. Pascal had been engaged and toward the solution of which he had just been making the final (and, in my opinion, correct) steps.

The confusion about the question of the behavior of the retinal vertical (and horizontal) axes and meridians during oblique oculorotations has been rather great, and in existence for quite some time. The observations and opinions of the classic authors have been reviewed many times and will not be analyzed here again. It was Prof. M. Márquez, of Mexico City, who, in the last decade, reviewed this

subject once more and offered his own solution. His contribution, however, rather than settling it, made the controversy more heated.

According to Márquez' analysis, the imaginary axis which vertically pierces the eyeball in its primary position (the "anatomical vertical axis," or the z-axis of Fick) tilts with its upper end backward and inward whenever the eye turns up and out. The imaginary transverse horizontal axis of the eyeball (the "anatomical transverse axis," or the x-axis of Fick) tilts at the same time with its outer end backward and downward.

Studying the diagram (Fig. 2), reproduced from Márquez, the observer has to think of himself as standing behind the right globe of a subject which around the axis RR' in Listing's plane (coincident with the plane of the paper) has turned upward and outward (temporally) to fixate point F'. The upper end-point (V) of the originally vertical diameter VV' describes a circle around the RR' axis

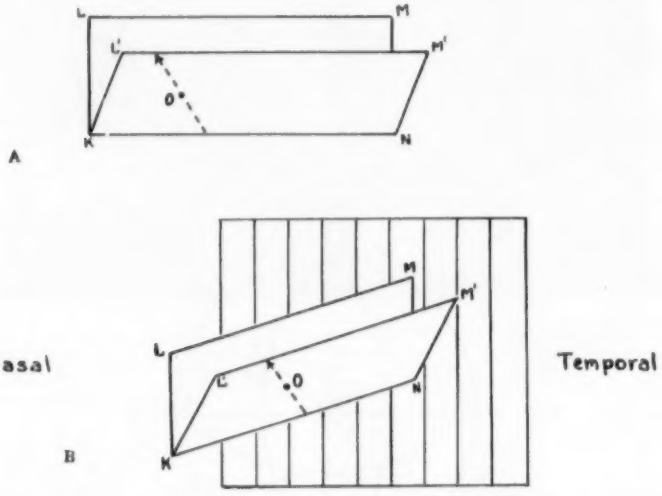

Fig. 5.—Perspective views of a tilted plane $KL'M'N$ and a slanting line (an arrow) in this plane.

during such movement (this is shown separately in Figure 3), while its upper half, VO, outlines the surface of a right cone with apex at O. By the time the gaze reaches F', the point V has arrived at M; the line VO has turned backward, nearer the observer, and M has become displayed inward, nasally, toward the subject's midsagittal plane. The temporal half (OH') of the originally transverse axis (HH') (Fig. 2) describes a similar conic surface around RR' and moves backward toward the observer, while at the same time tilting downward (Fig. 3). The point N', like point M, is nearer the observer. Naturally, the angle MON' continues to be an angle of 90 degrees, just as the original angle VOH' was, and statements to the effect that the transverse and vertical axes become inclined toward (or away from) each other, because the first "intorted" and the last "extorted," are bare of any real meaning. The anatomical vertical and anatomical transverse axes of the eyeball cannot become inclined toward each other, whatever rotations the eyeball has executed. It is only the projections of these axes upon a flat surface (the paper or

the photographic plate) which appear inclined toward each other on one side, and away from each other on the other side.

How little useful and how confusing descriptions in terms of "inward" or "outward" rotation can be becomes quite apparent as soon as those alleged tiltings of axes are not analyzed for themselves, but put into a broader context, e. g., compared with the projections of after-images. For this the image of a cross is impressed upon the anatomical vertical and horizontal meridians of the fovea P (see Fig. 4, taken from Márquez) while the eye is in its primary position. Now if this eye (again assumed to be the right eye) turns up and right to fixate some new fixation point F', then the after-image of the vertical line, now seen by the subject at F', is always tipped laterally on the top, no matter whether F' is a point on a flat, frontally located wall or a point on a concave sphere surrounding the subject (Ruete, Donders, Hering, Le Conte, Tscherning, Márquez, Verrijp, etc.). The reason for this is the inevitable tilting, the so-called false torsion of the anatomical vertical foveal meridian and the anatomical sagittal plane of the eyeball during oblique oculorotations, about which more is to be said presently. This plane starts at the now-tilted anatomical vertical foveal meridian, passes through the center of curvature of the eye O, through the apex A and the anatomical vertical meridian of the cornea, and hits the wall at F'. The plane hits the wall in an inclined manner, with its upper end outward. In no other way could the after-image appear upper end out (Márquez, Moses). But MM', the "inward" tilted anatomical vertical axis of the eye, must obviously lie within the tilted sagittal plane, just as it has been lying in this plane in its originally vertical position, while the eye gazed in the primary direction. The relationship of line and plane to each other could not have changed. Thus, MM' (Fig. 2) actually lies in a plane with upper end extorted. Only because the upper end (V) of the originally vertical axis (Fig. 3) came nearer to the observer, and moved behind Listing's plane, and nearer to the subject's midsagittal plane, does the projection MM' upon Listing's plane, or upon the plane of this paper, appear with the upper end intorted. Figure 5A and B should make this difficult point sufficiently clear. Figure 5A shows a true vertical plane, $KLMN$ (coincident with the plane of the paper), and a second plane, $KL'M'N$, which is tilted relative to the first (it is in front of the plane of this paper). In the second, tilted, plane, a slanting arrow is drawn through some point O in such a way that its tip is nearer to L'. Figure 5B shows the same two planes rotated counterclockwise (KL nearer the observer than MN), but seen by an observer whose position has not changed. Though the arrow still lies in the plane $KL'M'N$, tilted toward the right, the projection of the arrow on the flat wall behind the plane appears upper end tilted left. If one designates the two sides of the wall as "nasal" and "temporal," respectively, then one must state that the arrow is confined within a plane tilted upper end temporally, though in the projection on a wall its upper end appears tilted nasally.

The position of the tilted anatomical vertical axis MM' in Figure 2 can thus be characterized in the following manner: When the gaze turns upward and outward, the anatomical vertical ocular axis quite naturally remains contained within the anatomical sagittal plane, which passes through the anatomical vertical foveal meridian, the center of rotation, and the corneal apex and which, as a whole, tilts upper edge out. In the projection on any flat frontal plane, however, the upper end of the projection of this axis appears nearer to the midsagittal plane than the lower.

But even if this is conceded, one must add that calling the anatomical vertical axis of the eye intorted, while the eye looks upward and outward, adds to confusion rather than clarification of complex facts and is, at best, irrelevant.

Márquez' analysis of the behavior of the anatomical vertical and transverse axes of the eye, their "apparent movement . . . in opposite directions" has seemingly not occupied Dr. Pascal. The controversy in which he was engaged (and which, actually, he originated, since Professor Márquez, Dr. Pascal's intimate friend, became interested in the subject at the latter's instigation and request), centers around the behavior of the anatomical vertical and horizontal retinal and corneal "meridians," * while the globe turns in oblique directions, supposedly around axes in Listing's plane.

Based on a century-long study of the after-images of vertical linear impressions, there is quite general consensus that, as already mentioned in a previous paragraph, turning the eyes obliquely up and out, or down and in, causes extortion of the anatomical vertical foveal meridian (extorsion meaning temporal tilt of its upper end), while oblique gaze upward and inward, or downward and outward, causes intorsion of this structure. As to the behavior of the vertical corneal meridian, Márquez expressed the opinion in several papers that the upper end of this part of the anatomical vertical meridian of the eye intorts (tilts nasally) when the eye looks up and out, or down and in, and extorts (tilts temporally) in the other eventualities. These conclusions have not generally been accepted and were the actual concern of Dr. Pascal's last efforts. Studying details of the upper corneal limbus against a plumb line, Moses concluded that "on upward and outward gaze and on downward and inward gaze the eye [the vertical corneal meridian] extorts." He thus disagreed with Márquez; Pascal and Raubitschek at first both agreed with Márquez, while in later publications they expressed doubt as to the accuracy of his analysis.

In 1953, in a paper entitled "The Truth About False Torsion," Pascal came to the conclusion that "rotation of the eye on an axis in Listing's plane produces opposite displacements. . . . Thus in false torsion the meridians of the cornea and of the retina are inclined in opposite directions."

Raubitschek was, at first, of the same opinion. He stated that in oblique directions of gaze "the corneal meridians undergo opposite false torsion and that only the retinal meridians undergo torsion in the same direction." Only after Roelofs gave what to me seems to be impeccable trigonometrical proof that on upward and outward gaze the anatomical vertical corneal meridian actually extorts, have both Pascal and Raubitschek reconsidered their stand. Raubitschek's short, second, paper ends with the following English "Summary": "Contradictions in the papers of Roelofs and the author [Raubitschek] on the subject of 'false torsion' are explained and a trial is made to clear up the problem." And, according to Dr. Pascal's last published statement (March, 1955), "some new experiments more recently performed seem to show the contrary, namely that the corneal and retinal meridians rotate in the same direction, but possibly not to the same extent." In a letter, dated

* Actually, the problem deals with the behavior of limited sections of the vertical and horizontal ocular meridians within the confines of the cornea and fovea, respectively, or, in the strictest sense of the word, with the behavior of the vertical and horizontal diameters through these areas. However, the authors usually speak of foveal (or retinal) and corneal "meridians," and this terminology will be adhered to during the following discussion.

Nov. 16, 1954, and directed to Dr. William F. Hughes Jr., requesting exhibit space for the already mentioned exhibit, Dr. Pascal included the following brief outline:

The Corneal and Retinal Meridians in True and False Torsion

There has been some controversy recently as to the *declination of the corneal and retinal meridians.. relative to each other.* Some claim they tilt in the same direction; others claim they tilt in opposite directions. This exhibit, by means of models and charts showing the mathematical calculations, is designed to show that *they tilt in the same direction,* though possibly to an unequal degree.

The opinion of one of the several authorities approached by Dr. Pascal, Dr. Gerald Westheimer, of Ohio State University, is expressed in the following quotation:†

It looks to me as if Roelofs' description fits the known facts best. The eye rotating about an axis through the center of rotation and perpendicular to the plane containing the primary and tertiary directions of regard will arrive in a tertiary position with its vertical corneal and

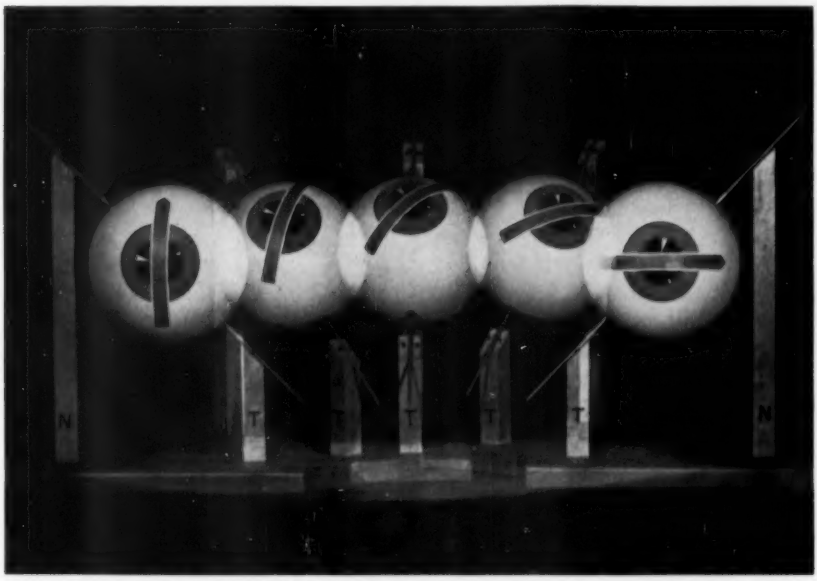

Fig. 6.—Composite photograph of an eyeball model rotating around an oblique axis in Listing's plane. Reproduced from Quereau, J. V. D.: Some Aspects of Torsion, A. M. A. Arch. Ophth. **51**:783, 1954, Fig. 2.

retinal meridians no longer coinciding with the true vertical as given by a plumb line. The direction of this "torsion" is excyclo if the tertiary position is up and out . . . and it applies equally to the retina and the cornea.

In Quereau's opinion (1954), too, eyes extort when looking upward and outward:

Suppose the left eye is to revolve about an axis 45 degrees from the vertical. As the cornea begins to move upward and outward, the vertical corneal meridian begins to undergo apparent extorsion. If the rotation of the eye would continue through 180 degrees, until the eye looked directly backward, the vertical corneal meridian would undergo 90 degrees of extorsion and become horizontal.

To illustrate this statement, Quereau published a composite photograph showing "a model of a left eye rotating around axis 45 degrees." This photograph is repro-

† Westheimer, G.: Personal communication to Dr. Pascal, Jan. 26, 1955.

duced (Fig. 6). The only change in the reproduction consists in the addition of the marks *T* for temporal and *N* for nasal, to identify these sides. The photograph on the extreme left is supposed to be one of the left globe in primary position, as seen from straight in front. The shorter of the two blocks supporting the oblique axis obviously represents the temporal side of the orbit; the longer block, its nasal side. The impression gained by the second photograph from the left is one of extorsion of the upper end of the corneal meridian. (It seemingly leans toward the shorter block, marked *T*.) This tilt seems to increase in each consecutive photograph. But as one arrives at the far right, one notices, to one's greatest surprise, that what Quereau described as the continued extorsion of the upper end of the corneal meridian by 90 degrees finally brought this end closest to N, the nasal side.

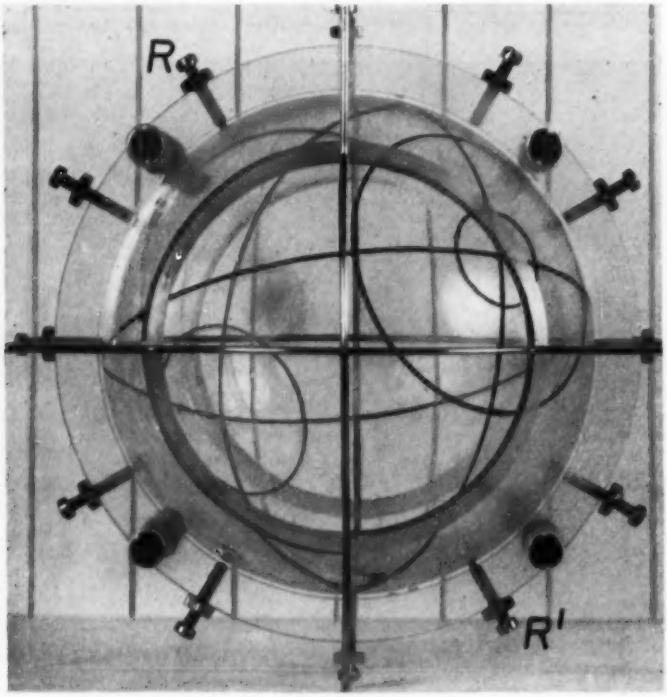

Fig. 7.—Apparent nasal displacement of the upper end of the corneal vertical meridian relative to vertical background lines, while the eye rotates up and out around an oblique axis in Listing's plane.

In fact, if the photograph proves anything at all, it proves that the corneal meridian has intorted, not extorted, as much as 90 degrees while the globe made one-half of a full rotation upward and outward around the 45-degree axis.

One cannot help but feel that there must be something basically wrong in the descriptions which lead to such contradictions between opinions of scientifically trained observers of renown, and even to such discrepancies as the one last mentioned. It has been shown above, in the example of Márquez' treatment of the vertical and transverse anatomical ocular axes, that the statement whether, say, the vertical axis intorts or not is not a statement to which the criterion true or false will apply. The same holds relative to the behavior of the anatomical vertical or

horizontal meridian through the cornea. One cannot dismiss as false or accept as true either of the opposing statements. Quereau himself emphasized repeatedly that statements of this type depend on the type of coordinate system one chooses to describe a certain change.

Photographs of a rotating eyeball or of eyeball models are, by the very nature of things, projections upon a flat surface of changes occurring on the surface of a sphere. Their pattern depends as much on the type of rotation imparted upon the eyeball as on the position of the camera. This should become clear by looking at another photograph (Fig. 7), one of the transparent eyeball model, devised by Pascal. The photograph is assumed to represent the left eyeball, turning up and

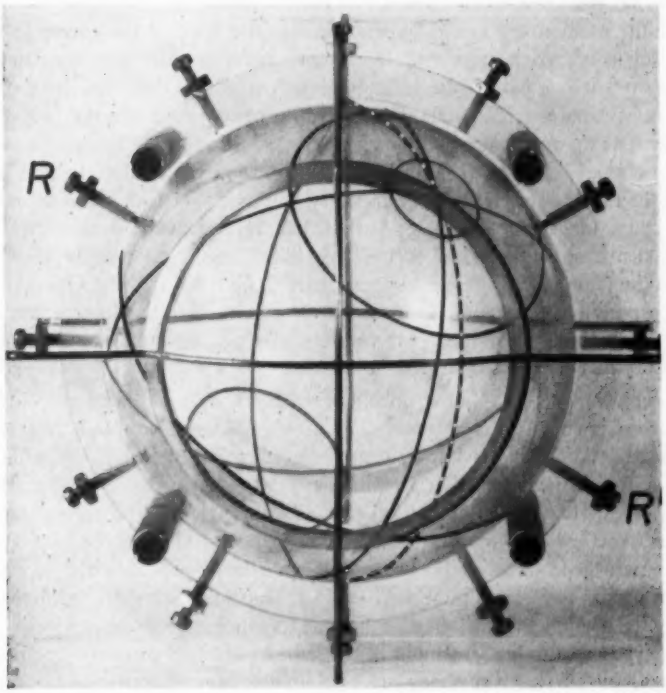

Fig. 8.—Actual temporal displacement of the upper end of the corneal meridian (continuous line) relative to the momentary vertical plane through the eyeball (dotted line), while the eye rotates up and out around an oblique axis in Listing's plane.

left, in a manner similar to that in Quereau's illustrations, but in this photograph the upper half of the corneal meridian shows a tendency to turn nasally. It does this, however, only because the rotated Pascal model has been photographed from in front, against a background of vertical lines, while Quereau changed the position of his camera for each subsequent shot and one's line of reference is inadvertently the longer of the two supporting bars. In any event, the photograph of the Pascal model seemingly justifies Márquez' contention that, in looking up and out, the vertical corneal meridian *in*torts, while all agree that the vertical foveal meridian *ex*torts at the same time. One, thus, cannot say simply that Márquez' statements are incorrect.

This type of representation loses, however, any value in settling the matter, once the question is asked for the criteria by which in- or extortion is determined. The criteria are quite simple if one tries to describe true torsion, i. e., the in- or extorsion of the vertical corneal meridian in the case of so-called wheel rotation around the anteroposterior ocular axis (the y-axis of Fick), the case in which corneal apex and fovea remain in their original place. In this case one compares the originally vertical meridian through the apex of the cornea (its anatomical vertical meridian) with a new meridian through the apex of the cornea, the momentary true vertical. Moreover, this momentary true vertical meridian is in the same locus of space which the anatomical vertical originally occupied. Answers in this case are quite unequivocal. But even if the eyeball rotated around some oblique axis in Listing's plane, so that the apex of the cornea and the fovea became displaced relative to the orbit and the momentary vertical plane through the apex of the cornea is not in its original locus of space anymore, in- or extorsion is still best determined with reference to such a plane. In fact, Roelofs suggested that the inclined vertical corneal and retinal meridians should always be related to a true vertical plane, the plane which at the moment of oblique gaze passes through the fovea, the cornea and the new point of fixation; and this, as Dr. Pascal in his final statement agreed, is the crux of the matter. If this momentary but true vertical plane is outlined on Pascal's eye model (Fig. 8), one finds that, looking upward and outward, the upper half of the anatomical vertical corneal meridian passes temporally to this plane, even if in the photograph the meridian appears to be tilted nasally. Quereau's photographs (especially the second from the extreme left) give the impression of extorsion of the corneal meridian, just because the photographs were taken in the approximate direction of these planes.

However, models or photographs cannot settle this problem any better than perspective drawings. In spite of Professor Márquez' unkind remarks about "pseudomathematics" in his last written communication to Dr. Pascal, this problem is essentially one in spherical trigonometry, and none of the several mathematical treatments of it have even suggested that the corneal and the retinal part of the anatomical vertical meridian of the eye could ever tilt in opposite directions. Roelofs' analysis is amazingly simple; Duke-Elder's, probably the most elegant. Elaborate proofs have been published by Hermann and Schubert. All these, however, require a good knowledge of spherical trigonometry to be understood, while Weiland's rather complex treatment of the subject is based on plane geometry. The most successful effort, in my view, to explain to nonmathematicians how the anatomical vertical ocular meridian tilts in the case of oblique ocular rotations, is that of Verrijp, in his contribution to the second edition of Berens' textbook. Following his discussion of this topic, one can study the behavior of both the foveal and the retinal anatomical vertical meridians simultaneously, and one finds, even without having to resort to formulas, that the alleged differences in their inclination are nonexistent. To make this demonstration more striking, Verrijp used the theoretically simplest, but in reality impossible, case of an eye turning a full 90 degrees up and to the right (Fig. 9). In contradistinction to Quereau's and Pascal's models, Verrijp's drawing is to be understood as representing an eye seen from behind, in a manner somewhat similar to Márquez diagrams.‡ *A*, the anterior pole, is away from the observer; *P*, the posterior pole, toward him. Rotation occurs along

‡ Actually, Verrijp's diagram places the observer in back of the subject's eye and somewhat toward the left; Márquez' diagram (Fig. 4), also in back but considerably to the right.

an axis RR' in the plane of the paper, coincident with Listing's plane. The corneal apex A moves into position A'; the retinal fovea P, into position P', both in the plane of the paper. Obviously, the upper end (V) and the lower end (W) of the anatomical vertical ocular meridian move at the same time in opposite directions. The half-axis OV outlines one-fourth of a right cone surface, and V comes in front of the plane of the paper, nearer to the observer, into position V'. In a similar manner, and by the same amount, W gets back of the plane of this paper, into position W'. The four points $V'A'W'P'$ determine the position of the anatomical vertical meridian at this moment. One-half of this meridian, from P' to A' through V', is in front of the plane of the paper, which, at this moment, coincides not only with Listing's plane but with the true vertical reference plane of Roelofs, the plane one has to lay through fovea, corneal tip, and fixation point F' if one

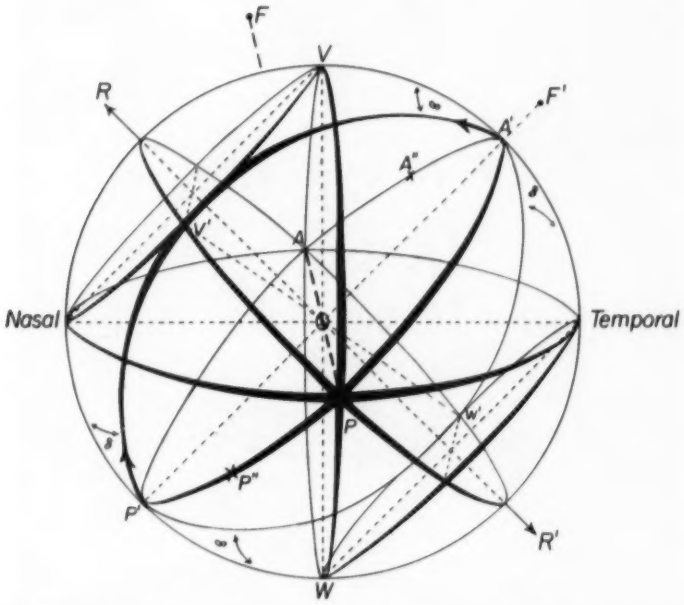

Fig. 9.—Perspective view (from the rear) of the anatomical vertical ocular meridian of a right eye rotated 90 degrees up and out around an oblique axis in Listing's plane. Reproduced, with modifications, from Verrijp, C. D., in Berens, C.: The Eye and Its Diseases, 1949, p. 699; published by W. B. Saunders Company, Philadelphia.

wants to make any rational statement about the momentary position of the anatomical vertical meridian during an oblique oculorotation. The anatomical vertical plane and the momentary true vertical plane meet in the line $A'OP'$, forming a so-called dihedral angle. The size of this dihedral inclination angle ($ROV'=R'OW'=\delta$) depends on two values: (1) the angle ROV, which the rotation axis in Listing's plane forms with the true vertical direction—it is an angle of 45 degrees in the case of the diagram— and (2) the magnitude of the excursion AA' (or PP') which the tip of the cornea (or the fovea) has made along the equator of rotation § $AA'PP'$—it is 90 degrees in the case of the diagram. The magnitude of δ has been deter-

§ The equator of rotation is an ocular great circle in the plane perpendicular to the rotational axis. It rotates around itself.

mined many times, among others by the above-mentioned authors. But whatever the actual value of this angle, the upper half of the anatomical vertical meridian through the cornea (marked by arrow) and the upper half of the anatomical vertical meridian through the fovea (marked by arrow) both must be inclined in the same direction relative to the true vertical plane, and by the same amount, since both are in the same tilted plane. (In the case of Figure 9, the half-meridian $A'V'P'$ is inclined toward the observer; it is neither intorted nor extorted but is in front of the plane of the paper.) Thus, Márquez' statement that the corneal and fovea verticals suffer opposite inclination remains a statement offering no essential information, in spite of its apparent correctness when one is viewing certain outlines or photographs.

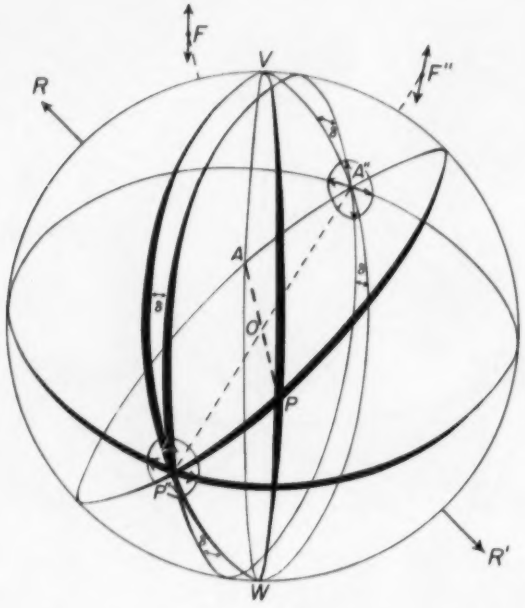

Fig. 10.—Perspective view (from the rear) of the anatomical vertical and horizontal meridians through the cornea and fovea of a right eye and of the tilted (originally vertical) afterimage seen by this eye while the eyeball rotates up and out around an oblique axis in Listing's plane.

The illustration given by Verrijp is obviously an extreme one. Only eye models can make a 90-degree excursion from the primary position to carry their gaze into Listing's plane. But even if one modifies Verrijp's exposition and assumes that A and P, respectively, have turned only as far as some point A'' and P'' (the positions indicated in Figure 9), matters will not be essentially different. V, the tip of the anatomical vertical axis of the eye, will in this case not turn as far as V' has turned, but it will still be in back of Listing's plane, nearer to the observer; and W, its lower end, will not turn as far as W' has turned, but it will again be in front of Listing's plane, away from the observer. The anatomical vertical meridian will thus again occupy a tilted position (Fig. 10), and the plane laid through it will hit the wall in front of the subject in an oblique line through F'', while Roelofs' plane (the true vertical plane laid through the fovea at P'', the

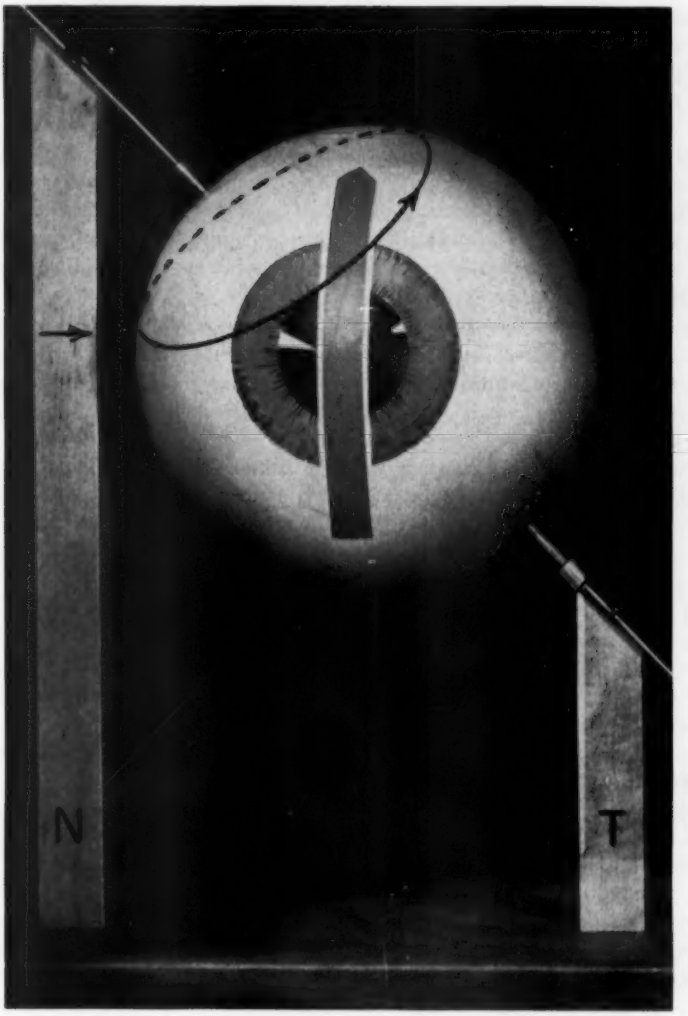

Fig. 11.—Path of the upper end-point of the anatomical corneal vertical meridian during oblique oculorotation around an axis in Listing's plane. Reproduced, with modifications, from Quereau, J. V. D.: A. M. A. Arch. Ophth. **51**:783, 1954.

center of rotation O, the apex of the cornea at A'', and the momentary fixation point at F'') occupies the position $VA''WP''$ and hits the wall in front of the subject in a vertical line through F''. The two planes meet in the line $P''OA''F''$. The sections of the anatomical vertical meridian which pass through the cornea at A'' and through the fovea at P'' are again indicated by arrows. Both lie obviously in the same plane and have the same inclination, δ, to the true vertical, just as in the illustrative case of Verrijp (Fig. 9). The only problem to consider is whether to call this inclination an extorsion or an intorsion.

Looking at A'' and P'' in Figure 10, one cannot help having the impression that both, the corneal and the foveal verticals, are intorted. But this is due only to linear

perspective, especially the choice of station point; and one faces the same situation as in the case of the tilted vertical axis. Both this diagram and Verrijp's have been prepared in the following manner: The observer is assumed to be in back of the subject's right eye and somewhat to the left (this is why he sees the vertical plane *AVPW* in the indicated foreshortened manner); his eye is the center of perspective projection (the so-called station point), and the projection itself is away from him, through the subject's eye, against the plane containing *F*. In such a projection, the corneal and the foveal vertical meridians of the up and outward turned eye appear tilted upper end toward left; they appear intorted, while the horizontal corneal and retinal meridians give at the same time the impression of being extorted (their temporal end is lower).‖

One must come to the conclusion that the whole argument about the behavior of the ocular meridians in terms of in- or extorsion would hardly be justified were it not for the behavior of after-images. A vertical linear image impressed upon the fovea while in the primary position causes an after-image with upper end tilted outward, if the eye rotates up- and outward¶ (or down and in). This extorted after-image is, in fact, in the same plane as the—in plane projection—seemingly intorted corneal and foveal vertical meridians of the rotated globe. One will thus conclude that in upward and outward rotation of an eye around an axis in Listing's plane both the corneal and the retinal meridians extort relative to Roelofs' plane, and to the same degree.

Although the problem appears thus to be settled, there is still one seeming contradiction to be resolved in connection with Quereau's illustrations (Fig. 6). As stated earlier, some of the photographs suggest that the upper corneal meridian extorts while the eye turns up and out. But when the model eye turned to the extreme of 180 degrees, it was found that the upper corneal meridian inclined nasally. (By the way, if the vertical meridian through the fovea were photographed after the 180-degree turn, it also would be found horizontal and its tip nasally inclined.) There is, however, no true contradiction. While the eye turns around the oblique axis of 135 degrees, the upper end of the corneal vertical meridian moves along the circumference of a circle which surrounds the axis, as indicated in Figure 11. Thus, this point, identical with the topmost point of the corneal limbus, will first appear to be moving away from the longer block (*N*), which represents the nasal side of the orbit. As rotation continues beyond 90 degrees, the same point of the corneal limbus will again approach block *N* (at least in the model, which, unlike the eye, can be rotated an unlimited amount). The point finally gets nearest to *N*, opposite the locus indicated by a small arrow. On further rotation, the same point of the corneal limbus starts again to move away from *N*, and as rotation finishes a full 360-degree turn, the meridian is vertical again and back in its original locus. Thus, the upper end of the corneal vertical meridian seems to suffer extorsion only at the beginning of the oculorotation, while the eye turns upward and outward. This extorsion turns into intorsion as the rotation continues around the same oblique axis. Actually, the movement is neither intorsion nor extorsion, in the true sense. As Raubitschek correctly emphasized, the upper end of the anatomical vertical meridian through the cornea describes a smaller circle of latitude around the axis than

‖ That the two sets of meridians are, and remain, at 90 degrees to each other, whatever their apparent "torsion," needs no further discussion. Their behavior parallels that of the vertical and transverse axes described in connection with Figure 2.

¶ It must be remembered that real eyes are able to make only limited excursions.

the apex of the cornea, which, lying, as it does, in the equator of rotation, outlines a great circle. The two points thus move at different speed, and this accounts for all the apparent torsional displacements of one against the other. Similar are the displacements of the upper end of the vertical meridian through the fovea. It will also move in a circle around the axis. Of course, it is getting closer to the nasal side of the orbit at first, and only later farther from it. And it also moves at a lower speed than the point we might want to call the geometric fovea. But whatever the complexities, the upper end of the vertical meridian through the fovea and the upper end of the vertical meridian through the cornea always are in the same plane, forming the same dihedral angle with the momentary true vertical plane, which passes through fovea, corneal apex, and momentary fixation point. By the way, the anatomical vertical axis of the eyeball lies in its entire length within that same tilted plane.

SUMMARY AND CONCLUSIONS

For all practical purposes, for the limited excursions the eye is actually able to make in oblique directions, it is justified to say that both corneal and retinal diameters extort when the eye turns upward and outward, or downward and inward, around an oblique axis situated in Listing's plane. They intort in the other eventualities.

Their false torsion is always in the same direction.

This confirms Dr. Pascal's last statement on the subject, according to which the anatomical vertical meridians through the fovea and through the cornea tilt during oblique oculorotation in the same direction. But one must add that they always tilt in exactly the same amount.

Dr. Harris Ripps collaborated in the planning and execution of the illustrations.

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A Bibliography of the History of Ophthalmology

1952 through 1954

CHARLES SNYDER
Boston

This bibliography of the history of ophthalmology has been compiled with the needs of two groups of readers in mind. The first group are those readers who want, from time to time, to spend hours of quiet pleasure exploring the past of the specialty of ophthalmology; for them this bibliography can serve as a reading list. The second group, scholars and medical historians, will find, it is hoped, that the bibliography is a tool that will spare them hours of tedious work.

The material is arranged under subject headings, and in two instances under subheadings as well. Standard abbreviations are used for the journal titles. Only articles that have appeared in medical and scientific journals have been included, and all these journals can be obtained in medical libraries in the United States. The titles of the articles have been translated into English, and the original language has been indicated by a capital letter at the close of the reference. Obituaries, always a valuable source of bibliographical data, have not been listed for doctors of the United States, although the obituaries of a few outstanding European ophthalmologists have been listed. Everything in the bibliography has been read in its original form whenever possible, and, when not possible, abstracts have been read instead. Thus, it can be said that, while not all the articles are entirely of an historical nature, they all do contain material that, broadly speaking, is a contribution to the history of ophthalmology.

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Visual Acuity Decrease at Various Illuminations and Role of Reading

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This research was prompted by the lack of quantitative and statistically significant evidence of deterioration of visual acuity in the course of prolonged visual work, despite subjective reports of tiredness. Earlier experimental efforts to produce such evidence were fruitless.*

In a previous study [5] it was shown that the course of visual fatigue can be determined accurately in terms of quantitative measures of performance if the test stimulus itself, i. e., Landolt's broken circle, is used as measure, as well as the fatiguing stimulus. Such a testing situation is comparable to the situation in experiments on muscular fatigue, in which the weight lifted is both the measure and the cause of fatigue.

The present experiments have been performed in order to ascertain whether the decline in visual acuity continues in the course of repeated series of determinations (cumulative fatigue) and how it is affected by illumination level and reading.

METHOD

With his head held in position by a chin rest, but with permission to move his eyes and blink, Subject O sat before a white background subtending a visual angle of 10 degrees and viewed a broken ring monocularly through an artificial pupil 2 mm. in diameter. The apparatus, previously described,[6] permitted automatic variation of the distance between O and the test object at a constant velocity of 5 cm. per second. To register his reports (recognition or disappearance of the gap in the ring), O pushed a button which operated an electromagnetic perforator. Retinal illumination and adaptation were held constant (at 8, 2, and 0.25 lux, respectively); the light source was controlled by a Sörensen voltage regulator and a lux meter. For a period of 60 minutes the subject made a continuous series of acuity determinations (half in ascending order, half in descending order), after which there was a 5-minute period of rest in the dark. A series of 20 additional determinations followed. Immediately after the latter, the subject read for 30 minutes (at retinal illuminations of approximately 9, 5 and 0.1 lux, respectively) with both eyes and without artificial pupil. This procedure was then repeated twice for each level of illumination, each session immediately following the preceding one. The results for two normal subjects are shown in the Figure *A* and *B*, each point there plotted being the mean of 10 determinations; the standard deviation (S. D.$=\sqrt{\frac{\Sigma\, d^2}{n\,(n-1)}}$) of each group is indicated at the bottom of each curve.

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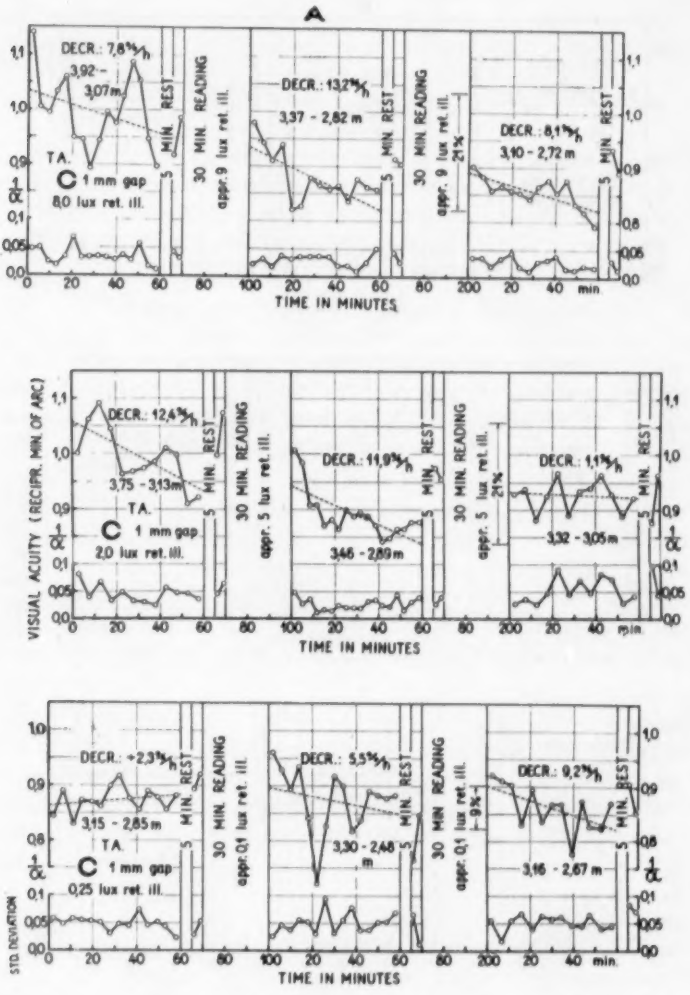
RESULTS

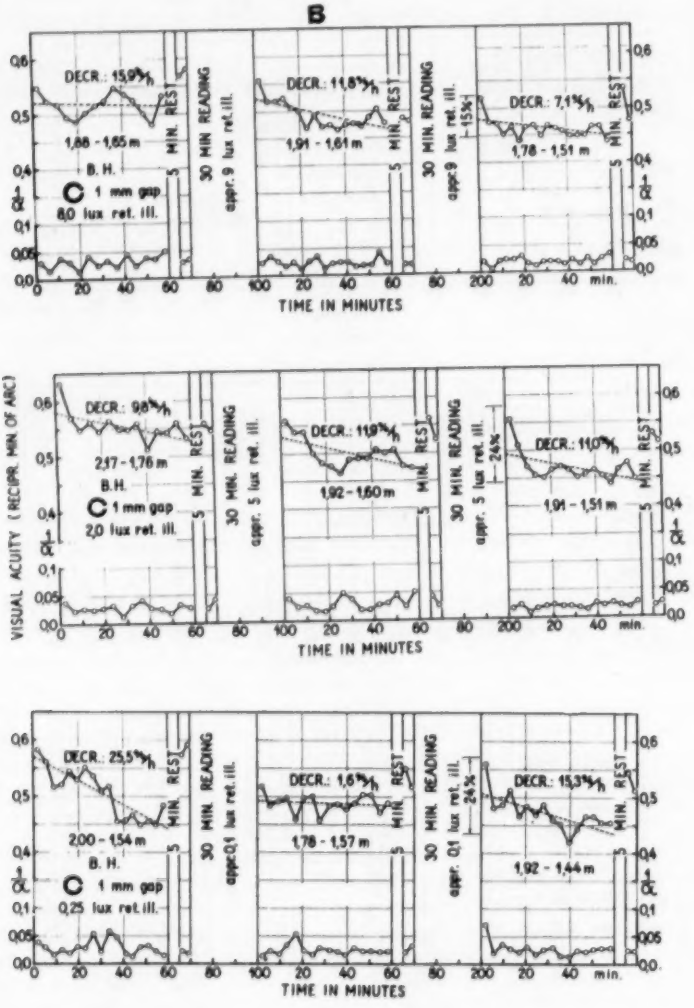
Decrease of Visual Acuity.—During 17 of 18 sessions of repeated monocular determinations, lasting one hour, visual acuity decreased significantly, the slopes ranging from 1.1%/L to 25.5%/L (Fig. *A* and *B*).



Cumulative decrease of visual acuity in the course of repeated series of measurements at various levels of illumination and the role of reading.

Recovery.—After five minutes' rest in the dark, immediately following the fatiguing period, acuity increased again in 15 of 18 cases. In six cases recovery was incomplete (between 13% and 86%); in nine cases, recovery was 100% or above. The latter cases indicate fatigue before the starting of measurements and pose the problem of which level of visual acuity in one subject may be assumed

to be "normal." Recovery cannot be attributed to dark adaptation during rest, because there was no significant general tendency of the measurements after rest and the adaptation level was the same before and after rest. The process of sensory adaptation is fundamentally different from fatigue and recovery.[7]



Cumulative Decrease of Visual Acuity.—In 9 of 12 successive experimental sessions (Fig. *A* and *B*) the decrease of visual acuity reached a significantly lower level in the second series than in the preceding one, in spite of the fact that a five-minute rest period in the dark plus 30 minutes' reading separated the two. This cumulative decrease of visual acuity continued in two cases through all three successive sessions of one-hour acuity measurements, being an average of about 18% for both subjects.

Illumination.—There was no consistent effect of illumination level upon the measured decrease of visual acuity in either subjects. The total cumulative decrease of visual acuity for one subject was highest when illumination was highest; with the other the opposite was true.[8]

Reading.—Thirty minutes of reading between two successive fatiguing periods in 6 of 12 cases had no effect upon visual acuity, irrespective of level of illumination. In three cases acuity increased and in three it decreased after reading. On an average, reading had no significant effect upon visual acuity, irrespective of the illumination level applied.[8]

COMMENT

The above-described evidence of a cumulative decrease of visual acuity in normal subjects during repeated monocular determinations may be an important link in the search for the yet unknown origin of myopia, since visual acuity and the refractive error of the myopic eye are highly correlated.[9]

If monocular visual acuity decreases with the above-described visual work significantly and in a cumulative way over a period of hours, it might be similarly affected over days, weeks, months, or years with many other visual tasks when both eyes are used. If five minutes' rest in the dark in many cases has not led to a complete recovery, a few hours' sleep after an entire day of "visual fatigue" might not lead to complete recovery either.[10] Reading, as corroborated by the above experiments, does not directly affect the visual mechanism, whereas watching the Landolt ring in motion does. This finding might be explained by the fact that in the first case above-threshold stimuli are recognized as meaningful, while the second case implies a continuous effort to watch a very small detail until it disappears and vice versa. The second case, therefore, represents a visual effort, the effect of which is measured, before recovery can be effective. The key to the problem of the origin of myopia may be lack of recovery and lack of knowledge of its nature. Reading and other visual tasks, while not causing a decrease of visual acuity, might hinder restitution.

The continuous change of distance (between 1.44 and 3.92 meters) between object and eye in the accommodation range, during the measurements, suggests that the described decrease of visual acuity is mainly fatigue of the tissues in the accommodation mechanism. Rest periods, as described above, can be applied in schools and factories without harm, and their effect should be studied, especially in cases of beginning myopia.

SUMMARY

On the principle of muscular experiments, in which the weight lifted is both the measure and the cause of fatigue, a cumulative and significant decrease of visual acuity (average slope about 18%) in the course of repeated series of monocular measurements with Landolt's broken circle is described. Various levels of illumination and intervals of half-hour reading had no unequivocal, significant influence. After five minutes' rest in the dark, the loss was partly or totally recovered. The possible relation of these facts to the etiology of myopia is discussed, and it is suggested that the nature of the restitution process may be the key to a new theory of the origin of myopia. Reading and other visual tasks may hinder restitution, thus contributing to the development of nearsightedness.

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Clinical Notes, New Instruments and Techniques

A TRANSILLUMINATOR FOR USE WITH THE CURVED GEIGER COUNTER

An Aid to Localization of Posterior Intraocular Neoplasms

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AND
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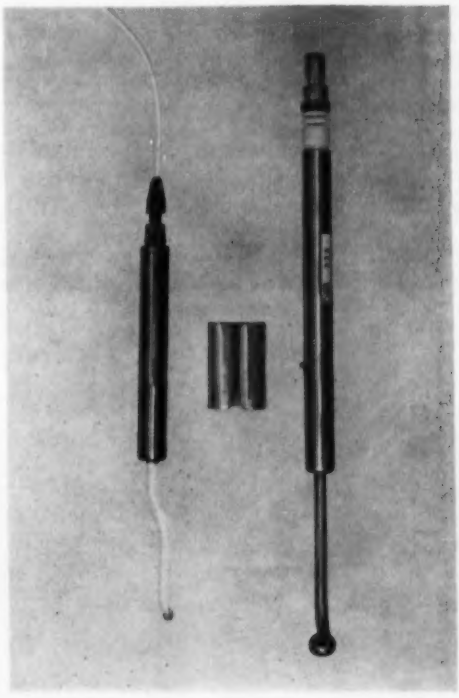
AS OUR studies on uptake of radioactive phosphorus by intraocular tumors have progressed, numerous technical modifications have been introduced to facilitate such measurements in posteriorly situated neoplasmas. A curved-angle-window Geiger counter was designed to be inserted through a conjunctival incision.[1] Later, in working with animals' eyes, a similar counter of smaller size was de-



A transilluminator for use with the curved-angle-window Geiger counter as an aid in localization of posterior intraocular neoplasms. Manufactured by Anton Electronic Laboratories, Inc., 1226-1238 Flushing Ave., Brooklyn 6.

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veloped, which is now also being used in clinical cases.[2] To aid further in the localization of posteriorly situated lesions, we have now constructed a transilluminator which is attached directly to the counter probe.

To obtain satisfactory radioactive counts over an intraocular lesion, the mica window of the counter must be placed as nearly over the tumor as possible; or at least, a border of the neoplasm must approximate the counter window. Accuracy in applying the counter to the scleral surface directly over the neoplasm depends upon precise knowledege of the anatomy of the eye and orbit and proper correlation with ophthalmoscopic findings. When the counter must be inserted through a conjunctival incision to the posterior portion of the eyeball, direct visual control is lost. Therefore the transilluminator has been designed to give some visual aid in more precise determination of the scleral area over which the counter should be placed. It is small enough to be inserted through the conjunctival incision and is attached to the counter probe with its illuminating end immediately adjacent to the mica window (Figure).

After the instrument has been inserted through the conjunctival incision to the region of the posterior bulbar surface where the neoplasm is presumed to exist, the room is darkened and the transilluminator is moved over the scleral surface until the shadow of the neoplasm is observed. The distance between the mica window and the tip of the transilluminator must be kept in mind in shifting the instrument a few millimeters into proper position for counting—that is, so that the mica window replaces the transilluminator tip. With this maneuver, it may be safely assumed that the counter is directly over the area to be examined. Counts may be taken in various additional locations to compare with that immediately over the area of retinal detachment.

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A NEW ENTOPTOSCOPE

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IN A PREVIOUS article [1] on Scheerer's phenomenon, we stated how, in the course of our research and after many trials, we had succeeded in building a simpler and better apparatus for its observation.

Scheerer's phenomenon is the entoptic perception of one's own blood cells circulating in the perimacular capillaries and the closest precapillary arterioles and postcapillary venules. We refer to the luminous points as blood cells, refraining from designating them as white or red, since this is still a moot question that has received contradictory answers from various authoritative sources. There is no doubt, however, that the phenomenon is connected intimately with the blood circulation.

The instrument * consists fundamentally of a metal box containing a mercury-vapor grid and a diffusing screen. On the upper part of the box there are two openings through which the light is seen. In the oculars there are filters that permit the passage of rays of only a determined wave length. There is also a forehead rest, which can be raised or lowered. A simple double occluder permits the use of one eye at a time and a quick comparison of the two. One of the oculars is fitted with a diaphragm suitable for the determination of Maxwell's area (avascular area). The box rests upon two inverted V-legs and can be tilted as desired.

The patient is instructed to look into the ocular with one eye and to tell what he can see at one glance; then the occluder is shifted, and he is asked to repeat the observation with the other eye. The possible responses are as follows:

1. The patient reports 20 to 25 cells with a pulsating motion—normal response.

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* Manufactured by Alfred P. Poll, 40 W. 55th St., New York.

Fig. 1.—The entoptoscope.

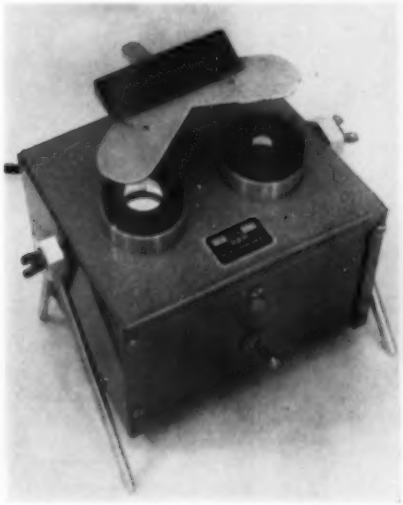

Fig. 2.—Patient at the entoptoscope.

2. The patient may report (*a*) fewer cells in one eye than in the other, (*b*) corpuscles in uniform motion, and/or (*c*) a decreased number of cells in one sector. These are abnormal responses.

3. The patient reports no cells—the most abnormal response of the three.

The Scheerer phenomenon is not a difficult one to perceive, requiring only some observation and no great amount of intelligence. It demands far less power of concentration than does a visual field.

We found that not all patients were able to report whether the movement of the dots was jerky or uniform, but all without exception were able to estimate the number of dots. The precise figure is less important than the comparison of the two eyes. A decrease of luminous dots in one eye indicates an angiospasm and is present long before a definite ophthalmoscopic change can be found. Maxwell's area is the more difficult to observe and therefore has less clinical importance. With a good observer it can give additional interesting information.

Scheerer's phenomenon can be used not only for clinical observation but also for the study of sedatives and peripheral vasodilators and their comparative pharmacodynamic action on the retinal circulation.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

CONJUNCTIVAL MYIASIS WITH OESTRUS OVIS LARVAE

INFESTATION of the eyes by the larvae of flies is not uncommon in tropical regions, but it is quite unusual and interesting when this kind of infestation occurs in the northern regions of the United States. Two such cases of conjunctival larval infestation have been reported by Sniderman [1] and Hedges and Humphries.[2]

The following case is a report of infestation of the conjunctival sac of one eye by the larvae of the sheep nasal botfly, Oestrus ovis.

REPORT OF CASE

A white man 30 years of age walked outside of a Naval Ordnance building at the outskirts of the city to eat his noonday lunch. As he sat down, a fly struck his right eye. Because the eye felt as if something remained in it, he reported to the plant dispensary at 12:30 p. m., where he was seen by a Naval Hospital Corps man and nurse, who examined the eye. No remnants of the fly were noted in the eye. In a short while the patient had a sensation of "worms" crawling in his eye. The nurse removed one moving object from the eye and then called the physician in charge of the dispensary, who noted something moving across the cornea. He removed three of the "worms."

Larva of sheep nasal botfly, Oestrus ovis, removed from right eye.

Received for publication Dec. 19, 1955.

I first saw the patient about 2:30 p. m. and, on separating the eyelids, noted a tiny white object with a black dot at one end moving quickly across the cornea. After instillation of a local anesthetic, one such object was removed and studied under the microscope and found to be a larva of the sheep nasal botfly, Oestrus ovis.[3] In the next three hours, eight more larvae were removed. The patient was sent home and instructed to call me if he felt any more movement "like worms" in the eye. At 7:30 p. m. he called and stated he felt certain there were two more "worms" in the eye. He was reexamined, and two more larvae were removed. After this, the eye remained comfortable, and the patient felt no more sensation like that originally experienced. The patient has been observed periodically since and is apparently free of myiasis.

SUMMARY

Conjunctival infestation of the right eye with larvae of the sheep nasal botfly, Oestrus ovis, is described.

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Annual Reviews

DISEASES OF THE UVEAL TRACT

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THIS REVIEW of the important available papers on disease of the uveal tract covers the period from October, 1954, to October, 1955. Several articles are included which were omitted from the previous Annual Review. The text will emphasize the reports which, in my opinion, have been the most noteworthy contributions to the advancement of knowledge in this field.

CONGENITAL DEFECTS

Cadenas Ugidos [1] reports the case of a 3-month-old boy with multiple congenital anomalies, consisting of bilateral total aniridia, macular aplasia, nystagmus, and umbilical hernia. François[2] describes a family showing throughout four generations the following defects: unilateral anophthalmos, unilateral microphthalmos with glaucoma and cataract, bilateral microphthalmos and blindness, unilateral coloboma of the iris, bilateral anophthalmos with the adiposogenital syndrome of Bardet-Biedl and mental disturbances, and a case of right-sided coloboma of the choroid and optic nerve. The mode of inheritance in this family suggested an irregular dominant rather than a recessive form.

DEGENERATIVE AND CIRCULATORY CONDITIONS

Iridoschisis.—This rare condition occurs as a rule only in elderly patients. An unusual case, the 14th reported in the literature, is described by Seidler-Dymitrowská and Dzierzykraj-Rogalski.[3] A young person without history of any other difficulty was found to have microcornea and separation of the anterior layers of the iris. The authors presume the iridoschisis to be congenital. Trevor-Roper [4] reports iridoschisis appearing in a 63-year-old woman who had had interstitial keratitis in childhood. The sphincter regions were intact, but elsewhere there was atrophy of the iris, with the formation of radial lacunae. The appearance was as though the outer material of the iris was fluffing into the anterior chamber.

Essential Atrophy of the Iris.—De Ferrari [5] reports a case of this condition with secondary glaucoma. Although the tension had been controlled by an iridosclerectomy for three years at the time of the report, the atrophy of the iris continued to progress. Kamel [6] describes a case in which the glaucoma was successfully treated by a double cyclodialysis operation. De Conciliis [7] describes a case which he believed represented a neuro-negative dystrophy secondary to tuberculosis. Healing followed treatment with aminosalicylic acid U. S. P. (PAS) and streptomycin. An unusual bilateral case is reported by Sivasubramaniam and Hoole.[8] A healthy 26-year-old man, whose vision was reduced to light perception, had bilateral buphthalmos associated with essential atrophy of the iris. Gonioscopy revealed peripheral anterior synechiae which blocked the angle of the anterior chamber. Another case of essential atrophy is reported by Georgiades.[9]

Recorded for publication Dec. 20, 1955.
From the Department of Ophthalmology, Emory University School of Medicine.

An interesting report is given by Alaerts,[10] who found that in 224 cases of primary glaucoma the atrophy of the iris was practically always present on the temporal side of the iris and only rarely involved the nasal or inferior quadrants. Alaerts favors a vascular origin for the iris atrophy in primary glaucoma but cannot account for its invariable occurrence in the upper temporal quadrant.

Familial and Hereditary Degeneration.—Study of three families exhibiting generalized choroidal sclerosis suggests to Sorsby and Davey [11] that the condition is inherited as a dominant trait. The probable course of the disease is as follows: (*a*) mottling of the central areas with a frequent edematous-hemorrhagic appearance; (*b*) intensification of the central reaction with pigment proliferation, (*c*) exposure of the choroidal vessels centrally with conversion into white streaks, (*d*) spread of the central lesion toward the periphery, and (*e*) absorption of the exposed sclerosed choroidal vessels, producing an appearance reminiscent of choroideremia.

Sandvig [12] reports a pedigree showing a condition which he calls central areolar choroidal atrophy of autosomal dominant inheritance. There was direct transmission over four generations. Transmission was by members of either sex, and there was no difference in the sex affected.

Evans [13] describes a case of paraplegia and choroidal atrophy in which there was a strong family history of paraplegia and blindness.

Alagna,[14] in reporting a rare case of gyrate atrophy of the choroid and retina, states that the condition must be distinguished from pigmentary degeneration of the retina, primary diffuse sclerosis of the choroidal vessels, and choroideremia. He states that true choroideremia and total congenital coloboma of the choroid represent identical congenital malformations, while the total or partial absence of the choroid in gyrate atrophy is only one of the main anatomicoclinical aspects of the degenerative choroidal process. Alagna believes that the origin of gyrate atrophy lies in a congenital, hereditary lability of the choroidal vascular system and that sclerosis of these vessels produces disappearance of the pigment epithelium and retinal atrophy.

INFLAMMATIONS

General Considerations.—In the general discussion of endogenous uveitis at the XVII International Congress of Ophthalmology in Montreal and New York, Woods [15] reiterates the view that so-called "granulomatous" and "nongranulomatous" uveitis represent two disease entities with different pathogeneses and clinical courses. He admits that this view is open to criticism in that pathological terms are being used to describe clinical entities and even histological differentiation may sometimes be impossible. According to this theory, endogenous granulomatous uveitis is believed to be the result of a direct infection of the eye by various specific causative agents. Woods gives the clinical, bacteriological, and histological evidence supporting this premise, reviews the clinical course and pathology, and advances an etiological classification of granulomatous inflammation of the eye.

Endogenous nongranulomatous uveitis, on the other hand, is believed to be the result of a sterile insult, which may be physical, toxic, or allergic. In most cases it is allergic and dependent on an underlying bacterial hypersensivity. Woods gives the clinical, experimental, bacteriological, and immunological evidence supporting this hypothesis and reviews the clinical course and pathology of nongranulomatous uveitis. He states that the difficulty in clinically and histologically differentiating the complicated forms of these inflammations arises from the fact that in basic granu-

lomatous uveitis there may be a superimposed allergic nongranulomatous reaction, and in nongranulomatous uveitis, where the allergic insult is prolonged, both the clinical and the histologic picture may simulate a granulomatous process.

Ashton [16] believes that the classification of uveitis into the "nongranulomatous" and "granulomatous" types is unsatisfactory because the histological reactions are simply those of acute and chronic inflammation and no sharp distinction can be made between them. He believes that attention has been too narrowly confined to allergic mechanisms in which organisms, such as the Streptococcus and the tubercle bacillus, are directly involved, whereas other endogenous disturbances may be of great significance. He cites as an example the fact that host proteins may be modified by reacting with circulating antibodies or by injury or combination with bacteria or their products. An inflammatory reaction may ensue, either through the formation of autoantibodies or through the direct stimulation of a "foreign-body" reaction.

In an analysis of the records of 200 cases of uveitis, Ashton [17] finds that there was a higher incidence of anterior uveitis in females than in males and that there was an earlier onset of posterior uveitis in males than in females. In his series anterior uveitis seemed to show a closer association with high antistreptolysin titers and cutaneous sensitivity to tuberculoprotein, whereas posterior uveitis was associated more frequently with serological results suggesting Toxoplasma infection.

Dekking [18] makes a critical review of current ideas on the etiology of uveitis and believes that only in syphilis, gonorrhea, focal infection by streptococci, and leptospirosis can the etiology in a given case be anything more than conjectural. He criticizes the acceptance of rheumatism as a satisfactory etiological diagnosis. The author also gives the results of his tests to O- and L-agglutinins in a group of 120 cases.

Cavara [19] discusses the clinical symptomatology, pathogenesis, diagnosis, and treatment of those uveal inflammations of supposed viral origin. He lists these conditions as follows: mucocutaneous-ocular syndromes (Reiter's disease, Behcet's syndrome, Stevens-Johnson syndrome); uveomeningitic syndromes (syndromes of Vogt-Koyanagi, sympathetic ophthalmitis); uveoreticuloendothelial syndromes (Besnier-Boeck-Schaumann disease, Heerfordt's syndrome, Hodgkins' disease).

Kravitz [20] presents 12 cases of iridocyclitis which he followed for several years. In all these cases gonioscopic studies were performed. Kravitz concludes that inflammations and infections of the anterior segment of the eye cause permanent changes in the angle of the anterior chamber, that pigment deposits in the trabeculum do not cause glaucoma, and that increased viscosity of the aqueous may have some bearing on the increase of intraocular tension.

Cross [21] analyzes a series of cases of uveitis in patients under 16 years of age. He finds that in patients with anterior uveitis acute specific fevers cause uveitis more frequently than is actually seen. Congenital syphilis and sarcoidosis are only rare causes of anterior uveitis in children. The incidence of tuberculosis is difficult to determine accurately. Other occasional causes are Still's disease, brucellosis, and the Vogt-Koyanagi syndrome. He finds that the chief causes of posterior uveitis in children are toxoplasmosis and tuberculosis. The solitary exudative type of posterior uveitis is not uncommon, but its cause is obscure. In children a panuveitis is most commonly caused by sympathetic ophthalmia. A nonspecific panuveitis is sometimes seen in cases of optic neuritis, and in these the use of corticotropin is helpful.

Bouzas [22] believes that the albumin and cell content of the aqueous, as obtained by anterior chamber puncture, can differentiate acute, subacute, and chronic inflammation of the anterior uvea, and that by it the deceptive apparent improvement produced by cortisone can be unmasked.

Three Polish authors, Ogielska, Skurski, and Ogielski * investigated the bacterial flora in the aqueous humor in cases of iridocyclitis, and, although they found staphylococci in only about 4% of the cases, the conjunctival flora showed more virulent staphylococci than were present in the control cases. By using the color reaction described by Kolobocki, these authors demonstrated an increased production of toxin (probably staphylococcal) in both the anterior chamber and the conjunctiva. This suggests to the authors a relation of the pathological process in the iris to the kind of micro-organism in the conjunctiva.

Experimental Studies.—Goldmann and Witmer [25] report on the relative antibody levels of aqueous and serum in various infections. In leptospiral uveitis of horses, the specific antibody was found to be increased in the aqueous, and higher than the level in the serum. This increase can be explained only by antibody formation in the diseased ocular tissue. In experimental tuberculous infections in the eyes of rabbits, the antibody titer was higher in the aqueous than in the serum if the ocular infection was primary. If, however, the ocular infection was secondary to generalized tuberculous disease, the antibody content was lower in the aqueous than in the serum but showed a relative increase, i. e., more than could be accounted for by diffusion from the blood. Using the Middlebrook-Dubos method, the authors found that the tubercle antibodies of the aqueous were increased in patients with uveitis of probable tuberculous origin, as compared with the levels obtained in nontuberculous cases.

Alfano and Clampit [26] refute previous experiments which showed that iritis was produced in the rabbit eye by the injection of hyaluronidase into the anterior chamber. When a different preparation of the same drug was used, no adverse effects occurred.

Tuberculosis.—The Middlebrook-Dubos hemagglutination test for tuberculosis has been found useful in the diagnosis of ocular tuberculosis, according to the reports of Galli [27] and of Cremer and Cremer.[28] The latter authors found the test positive in 63 out of 85 cases of tuberculous eye affections of various types. The titers in these cases were approximately 1 : 16, and a fluctuation of the clinical condition was reflected in the titer concentration. In four cases of sarcoidosis with uveitis a positive reaction was also obtained, with average titers of 1 : 16. Niitsu [29] finds it useful to perform the test on the aqueous, since the reaction is positive only in ocular tuberculosis.

Bijneu [30] found that in two cases of iridocyclitis and retinal periphlebitis a biopsy of the liver helped confirm that the conditions were tuberculous in origin.

Hoel [31] reports the case of a 38-year-old man who had recently been vaccinated with BCG, and who developed a severe acute iritis, fever, and general symptoms following a tuberculin skin test for diagnostic purposes. Chavanne and Rougier [32] describe a patient who developed serous choroiditis of one eye and an exudative macular chorioretinitis of the other eye after BCG vaccination.

There are several reports on the efficacy of isoniazid (isonicotinic acid hydrazide) in the treatment of ocular tuberculosis, especially when used in combination with streptomycin or with streptomycin and aminosalicylic acid. The reports of large series of such cases are presented by Dubois-Poulsen,[33] Gergovich and Szantroch-Miszke,[34] Kesavachar,[35] Dolcet,[36] Medkova and Medek,[37] Velicky,[38] and Kratka.[39]

* References 23 and 24.

Kratka summarizes his studies as follows: Isoniazid, especially when combined with streptomycin, has a definite value in treatment of human ocular tuberculosis, and he obtained a cure in 56 out of 94 cases. Patients with posterior uveitis, and with periphlebitis and hemorrhage, responded best (65% were improved). The next best response was in anterior uveitis (52% improved). The drug is nontoxic and inexpensive. The dosage used by Kratka was 3 to 5 mg. per kilogram of body weight, and all patients received an average of 300 to 400 mg. a day (orally). In cases of anterior segment lesions isoniazid ointment (200 mg. per gram) was used topically at bedtime. In cases of uveitis the drug must be used three to four weeks before improvement can be expected, and must be continued for a minimum of four months to obtain a cure. Despite reports contraindicating the use of cortisone in tuberculosis, Kratka employed it in addition to isoniazid and streptomycin in a few cases and obtained good results. Cortisone is thought to inhibit the tuberculous inflammatory reaction, thus allowing isoniazid and streptomycin to attack the tubercle bacilli more rapidly.

In experimental systemic and ocular tuberculosis in rabbits, Witmer [40] compares the albumin and globulin values, as well as the hemagglutinins, of the serum with the corresponding values for the primary and secondary aqueous. In rabbits Doubrovena [41] produces histological, but not always clinical, eye lesions by sensitizing the animal with subcutaneous horse serum and then injecting tubercle bacilli intravenously.

Toxoplasmosis.—Cases of congenital toxoplasmosis are reported by Bartsocas [42] and by Mehta.[43] The latter suggests that, because younger siblings of his two patients were not affected, the parasitemia in pregnancy must be only transitory or neutralizing antibodies must be quickly formed in the maternal blood.

By means of the phase-contrast microscope Habegger [44] was able to demonstrate the living Toxoplasma organisms isolated from the aqueous of a 2-month-old patient showing no signs of anterior uveitis, and from the subretinal exudate in a 45-year-old woman.

Wagener [45] gives a comprehensive review of the present state of knowledge concerning toxoplasmic chorioretinitis in the adult. It has not yet been determined whether Toxoplasma can cause anterior uveitis, nor have criteria been agreed upon for the definite clinical diagnosis.

Jacobs, Cook, and Wilder [46] obtained blood serum from 21 patients in whom protozoa had been found on histological examination of the enucleated eyes. The Sabin-Feldman dye test was positive in all 21 cases, and in only 3 instances was the titer below 1:16. The authors conclude that the demonstration of the toxoplasmic etiology of uveitis must come from the isolation and identification of parasites from typical cases. They suggest that, apart from rising titer, only the dye tests which are completely negative can be considered really significant. The complement fixation test is of no value in the diagnosis of old infection.

In an analysis of 67 cases of granulomatous uveitis, Ryan and associates [47] made the diagnosis of presumptive toxoplasmic uveitis in 39 cases on the basis of positive skin and dye tests. Of these 39 cases, 29 showed evidence of activity and were treated with various regimens of pyrimethamine (Daraprim) and sulfadiazine. In 25 of the 29 cases clinical improvement occurred, but there are unpleasant and potentially dangerous side-effects during the use of pyrimethamine, making it necessary to use this drug only with great caution and under close supervision. The authors feel that skin testing with toxoplasmin has more possibilities for wide-

spread clinical use, since no patient in their series failed to give a positive dye test who had a positive skin test, no cases with a negative dye test showed a positive skin test, and 80% of the cases with a positive dye test showed a positive skin test.

Hogan [48] reports that the serological tests for toxoplasmosis are useful in helping to diagnose the disease in the first five years of life. After this time the antibody level drops and most diagnoses are presumptive. Relapse of the chorioretinitis does not seem to affect the dye-test titer. The chorioretinitis of ocular toxoplasmosis is not different from that due to other causes, although most lesions are large, produce heavy vitreous opacification, and tend to recur, as long as 4 to 25 years after the initial disease. In the diagnosis of adult toxoplasmic chorioretinitis, Hogan is skeptical of the significance of the skin tests and dye tests except in the case of a negative skin test, and he advises continuing the present custom of a general survey in determining the etiology of uveitis cases, employing the means at hand. Aqueous humor dye tests were of no value in the diagnosis of ocular toxoplasmosis. Hogan used pyrimethamine in a group in which the diagnosis of presumptive toxoplasmic chorioretinitis had been made and was disappointed in the results. The inflammatory foci did not appear to be affected.

Cassady, Culberton, and Bahler [49] tested the sera of 36 patients with vascular or inflammatory disease of the posterior uvea by means of the Sabin-Feldman dye test. The sera of 23 of these cases was positive for toxoplasmosis, while a survey for any other etiologic agent in their ocular inflammation was negative. In 7 patients the disease was inactive or quiescent, while in 16 it was active. Eleven of the patients with active granulomatous uveitis were treated with pyrimethamine and sulfadiazine systemically, producing a marked and dramatic improvement in the uveitis. The authors sound a note of warning that the treatment may be dangerous and should be used only where blood studies are carefully controlled. They also observed that, whereas cortisone allays most eye infections, it intensified the inflammation in two of their cases of toxoplasmic chorioretinitis, an observation described also by Ryan and by Passmore.

Frenkel [50] produces chronic generalized Toxoplasma and Besnoitia infections in hamsters and describes the localization, development, and extension of the ocular lesions incidental to these infections. Such experimental infections will represent models for comparison with sporadic chorioretinitis in man and will aid in the study of immunological and therapeutic problems of toxoplasmosis.

Relapsing Iridocyclitis with Mucocutaneous Lesions (Behcet's Disease).—This syndrome is a systemic disorder characterized by recurrent oral and genital ulcerations and relapsing iritis or iridocyclitis, which is accompanied by hypopyon. Since the three classic manifestations have not been present in every case, Curth [51] prefers to call the disorder "aphthosis," rather than Behcet's syndrome. Curth believes that a vascular disturbance is the underlying factor. According to Lemke,[52] the etiology is unknown and there is no specific therapy. Vascular changes, such as thrombophlebitis, are of value in the pathogenesis and prognosis; the author observed that they became worse after the use of corticotropin. The case of Cavara and d'Ermo [53] was complicated by troubles of the central nervous system and a left lateral hemianopsia—a symptom that had not previously been described in the eight cases of neuro-Behcet's syndrome reported in the literature. Sezer [54] isolated a filtrable virus from the blood serum of 10 patients during the fever stage of the disease. The appearance of the inoculated egg membrane was similar

to that reported previously by him, using eye material. Sezer also obtained a filtrate from the urine of these 10 patients and inoculated guinea pigs with it. Most of the injected animals died, but it has not yet been established whether from a virus infection or from a toxin produced by the virus.

Leptospiral Uveitis.—Okamune and Yamamoto † report on a series of 69 cases seen during the last two years. Four kinds of leptospirosis were differentiated serologically by the authors. The first appearance of the uveitis after clinical onset of the systemic disease varied from 20 days to 5 years. Almost all cases showed vitreous opacities sooner or later, and the posterior uvea was frequently involved. According to these authors and Offret and Saraux,[57] leptospiral uveitis is a relatively benign disease with usually a favorable outcome. Kubistova and Petru [58] report a case of bilateral iridocyclitis caused by Leptospira canicola. Witmer [59] experimentally produced a primary intraocular infection in rabbits with Leptospira pomona. Antibody formation in these experimental infections seemed to start at unknown extraocular sites, but after 14 days the antibody activity of the aqueous exceeded that of the serum by about 3:1, denoting local intraocular production of antibodies. These experiments confirm earlier reports on the probable local antibody formation in experimental tuberculous uveitis and in periodic ophthalmia in horses. The author also studied the eyes histologically. He found that plasma cells and lymphocytes appeared in the uvea on the 10th day of infection and coincident with the appearance of antibodies in the aqueous.

Uveitis Associated with Joint Disease.—Michaud and Forestier [60] found uveitis in only 17 patients among 200 cases of ankylosing spondylarthritis, an incidence which is lower than is usually believed to exist. The uveitis may appear before any joint symptoms and may be so mild at first as to be mistaken for conjunctivitis. The uveitis is at first nongranulomatous but may become granulomatous after repeated attacks and recurrences. Bonnet and Thiers [61] state that while the common ocular manifestation is a plastic iritis, lesions of the choroid and retina can occur, but may be overlooked, because of their peripheral position. In discussing Still's disease, François and Haustrate [62] state that bilateral insidious and chronic iridocyclitis, band-shaped corneal opacity, and complicated cataract in a child are pathognomonic of infantile rheumatism even in the absence of acute articular lesions. In a given case it is impossible to say whether the condition is Still's disease or chronic progressive rheumatism.

Sympathetic Ophthalmia.—Forchheimer [63] reports a case of bilateral sympathetic ophthalmia which subsided promptly after the local use of cortisone eye drops, but there was no histological verification of the initial diagnosis. Radnót [64] describes five cases treated successfully with local and systemic corticosteroids. A child with established sympathetic ophthalmitis reported by Somerville-Large [65] responded well to topical and systemic cortisone, but the relapse which followed withdrawal of the cortisone was resistant to further treatment. Georgiades and Petridis [66] report two mild cases, one cured by enucleation alone, the other by enucleation, antibiotics, and fever therapy. The case of Sakon [67] was not helped by corticotropin and cortisone and healing occurred only after treatment with large doses of bipenicillin (procaine penicillin G and buffered crystalline penicillin G potassium) and intravenous injections of cinchophen (Atophan). Bailbé [68] also stresses the necessity of combined treatment with corticosteroids and antibiotics in sympathetic ophthalmia,

† References 55 and 56.

and Streiff and Miescher [69] emphasize the infectious factor in the pathogenesis of the disease. Letson [70] reports a histologically proved case of sympathetic ophthalmia following basal iridectomy for acute glaucoma. The condition eventually responded to intramuscular corticotropin given daily for a period of six months. Redslob and Lobstein [71] review the literature on the problem of unilateral sympathetic ophthalmitis and report a case which was proved histologically. In the interesting case reported by Offret and Haye [72] enucleation of the injured eye was followed by deep uveitis and exudative retinal detachment in the other eye and by lymphocytic meningitis and labyrinthitis. Reviews and case reports on the subject of sympathetic ophthalmia are given by Tsopelas [73] and by Ikui and Furuyoshi.[74]

Few clinical studies of sympathetic ophthalmia involve a large group of cases. Winter [75] analyzes 257 cases, one of the largest number ever reported. In his series the visual result in the sympathizing eye did not correlate with a histological estimation of the degree of severity of the inflammation in the exciting eye or with its location primarily in the anterior or posterior uvea. The final vision in the sympathizing eye was considerably better when few epithelioid cells were present in the exciting eye and when pigment phagocytosis was light. The author urges against enucleation of the exciting eye.

Naquin,[76] in experiments on guinea pigs, is unable to confirm the results reported in 1949 by Collins, who, using macerated guinea-pig uvea and the so-called Freund-type adjuvants, produced lesions in the choroid histologically simulating those of sympathetic ophthalmia found in human eyes.

Syndromes of Harada and Vogt-Koyanagi. — Cordes [77] describes a case of Harada's disease, the 10th such case to appear in the American literature. In this case local and systemic cortisone did not seem to affect the course of the disease in any way. Swartz [78] reports an interesting case in which bilateral uveitis developed 12 days after an extracapsular cataract extraction. The patient ultimately developed alopecia, poliosis, vitiligo, and dysacousia. Systemic antibiotics were not helpful, and topical and subconjunctival cortisone was of only slight benefit.

Puig Solanes and Chevez [79] studied the enucleated eyes and biopsy specimens of skin in two cases of the Vogt-Koyanagi syndrome. These authors conclude that (*a*) the entire uveal tract is involved, especially the anterior portion; (*b*) the inflammatory process extends less intensely to the neighboring tissues; (*c*) the cellular infiltrate is predominantly lymphocytic and with plasma cells and becomes diffuse early in the disease; (*d*) there is marked tendency to fibrosis; (*e*) the skin biopsy specimens show a similar inflammatory reaction and changes in the elastic tissue, and (*f*) the pathology of the syndrome is undoubtedly different from that of sympathetic ophthalmia.

Other case reports of the Vogt-Koyanagi syndrome and of cases of uveoencephalitis resembling it are given by Robinson,[80] Pawelec,[81] Lopez Marin,[82] Gonzales,[83] Meauvieux and associates,[84] Alajouanine and associates,[85] and Riazi and Marshall.[86] Jacobius and Grandi [87] describe an interesting case of bilateral acute choroiditis and lymphocytic meningitis.

Thomas and associates [88] produced meningitis in rabbits and describe the chemical and biological modifications which appear in the aqueous humor, similar to those of the cerebrospinal fluid, occurring independent of any clinical symptoms in the anterior segment of the eye. This suggests the possible existence of cryptouveitis in meningitis, in addition to the common cryptomeningitis occurring in uveitis.

Heterochromic Cyclitis.—Franceschetti [89] describes his experiences with 62 cases of heterochromic cyclitis, pointing out that the diagnosis is not always easy. In the

early stages, disturbing subjective alterations of the vitreous associated with keratic deposits may suggest uveitis of another origin. The heterochromia may be slight or absent for a long time, and, exceptionally, the diseased eye may appear even darker than the fellow eye, owing to the posterior pigment layer shining through the atrophic stroma. The author states that bilateral heterochromic cyclitis is not as rare as is generally believed. François and Beheyt [90] report four such cases.

Pinchon [91] reports two cases in which heterochromic uveitis with cataract was associated with traumatic cervical lesions, and he believes the syndrome has a sympathetic nervous system origin.

Kimura, Hogan, and Thygeson [92] review the subject of heterochromic cyclitis and describe 21 cases, an incidence of 2%, in his series of 750 cases of uveitis of all types. The authors stress the insidious onset, the absence of any acute signs or symptoms, the lack of posterior synechiae, and the completely negative results obtained in the general survey of such cases. The heterochromia of the iris in this syndrome is easily distinguished from the patchy atrophy and discoloration which sometimes follow anterior uveitis of other types. The prognosis for cataract extraction is good. If the syndrome of heterochromic cyclitis can be recognized promptly, much time and expense can be saved for both the examiner and the patient, since none of the tests performed in the usual work-up of a case of uveitis is of any value in the diagnosis or management of this entity.

Georgiades [93] presents five cases of increased pigmentation of the iris associated with cataract, a syndrome not specifically described in the literature. The iris was examined histologically in four cases, and sclerosis of the vessels and iris stroma was found in all cases in addition to intense pigmentation.

Four cases of heterochromia iridis occurring in the Claude Bernard-Horner syndrome are reported by Gougnard-Rion and Paris.[94] Two cases were due to birth trauma, one possibly to toxoplasmosis and the other to an obscure cause. Heterochromia in this syndrome usually, but not always, occurs when the onset is prior to completion of pigmentation of the iris, about about 2 years of age.

Lens-Induced Uveitis.—Kronenberg [95] reports four cases of uveitis following cataract extraction in the eye not operated on. The eye operated on did not show any unusual inflammatory reaction. The treatment should be prompt removal of the lens of the intact eye.

Agarwal and Mehra ‡ performed skin sensitivity tests with lens protein and with cysteine on 300 cataract patients, comparing the results with the degree of postoperative iridocyclitis. The severity of the postoperative reactions was found to agree with the intensity of the positive skin test but not with the quality of lens material remaining after the extracapsular operation. The authors feel that the postoperative reaction is an allergic rather than a toxic one and that the cysteine amino acids should be held responsible. The lens protein and cysteine skin tests gave exactly comparable results, and the authors recommend that intracapsular extraction be performed on every patient with a positive cysteine skin test.

Other cases of lens-induced uveitis are reported by MacDonald [98] and Müller.[99]

Miscellaneous Inflammations.—Cohen and Chamblin [100] report a case of iridocyclitis associated with glaucoma and retrobulbar neuritis. A nerve-fiber-bundle field defect was present. The authors state that in the ophthalmic literature there is only one histologically confirmed case of iridocyclitis complicated by retrobulbar neuritis, namely, that of Weller.

‡ References 96 and 97.

Huggert [101] describes the uveal changes in four cases of Hodgkin's disease.

Cases of uveitis thought to be due to brucellosis infection are reported by Viallefont [102] and by Chavarria Iriarte.[103]

Spyratos [104] studied the aqueous cytology in a case of bilateral leprous iritis.

Hambresin [105] reports the case of a young woman with Quincke's disease, manifested by edema of the lower lip and breast and bilateral iritis. All treatment, including cortisone, failed until antihistaminic drugs were given.

Thomas, Vitte, and Guidat [106] report a case of acute iritis with hyphema occurring in a patient with lymphoid leukemia. Contact treatment with x-rays was successful in clearing the condition.

Therapy of Uveitis.—Antor [107] recommends the use of aminopyrine-phenylbutazone (Irgapyrin) in the iritis of rheumatic origin, as well as in postoperative ocular states and episcleritis. Szaloczi [108] gives the drug intravenously. Yourish and associates [109] report on the effects of phenylbutazone (Butazolidin) on experimentally induced ocular inflammation. Phenylbutazone is one of the component parts of Irgapyrin. These authors found that when the phenylbutazone is given intramuscularly in experimental animals, it is capable of blocking the inflammatory effects produced by glycerin injected into the anterior chambers of the rabbit eye, although it does not penetrate into the aqueous humor. The anti-inflammatory effect was found comparable to that obtained with cortisone. Application of phenylbutazone ointment locally was ineffective.

Hopen [110] reports on results obtained in 17 cases of ocular inflammation refractory to cortisone in which he had given trypsin by intravenous, intramuscular, or subconjunctival injection. Four of the eleven cases which responded satisfactorily were impressive, and the intramuscular route seemed to give the best results.

Von Nordheim [111] finds that naphazoline hydrochloride, a vasoconstrictory agent, when used in a concentration of 0.5% to 1.0% solution and combined with atropine, is a useful agent for dilating the pupil in cases of iridocyclitis.

Sutton and Beattie [112] report the case of a man of 35 who began to have blurred vision 10 days after beginning aminosalicylic acid U. S. P. 15 gm. a day and isoniazid 200 mg. a day. After two months on this regimen the patient developed severe optic atrophy. The patient had previously had streptomycin 1 gm. twice weekly and aminosalicylic acid 20 gm. daily for two months, without ill-effects. The authors presume that the visual effect was the result of an idiosyncrasy to isoniazid.

François [113] finds that local cortisone treatment in uveitis sometimes leads to ocular hypertension, which is usually only moderate, is not accompanied by any objective or subjective disturbance, and often appears after the cure of the uveitis. Laval and Collier [114] found a dangerously elevated tension in three proved cases of sarcoidosis after the use of cortisone, especially after the use of corticotropin. The authors feel that in these cases the uveitis alone was not enough to cause the increase in tension, but that steroid therapy is more apt to produce glaucoma in those cases having intraocular changes that hinder the normal drainage of intraocular fluid.

Wiemar and Leopold,[115] in experiments on rabbits, measured the intraocular penetration of topically instilled or subconjunctivally injected cortisone and hydrocortisone. These authors found that cortisone penetrated the anterior chamber in higher amounts than did hydrocortisone. Removal of the corneal-epithelial-barrier-induced inflammation increased the penetration of both agents. The need for more sensitive methods in the detection of steroids in the aqueous is stressed.

King and Weimer [116] report on a comparative study of the therapeutic value of prednisone (Meticorten) and prednisolone (Meticortelone), and cortisone and hydrocortisone. It is the conclusion of these authors that the newer corticosteroids may entirely replace cortisone and hydrocortisone in ophthalmology, as their action is less toxic, more rapid in action, and effective in low maintenance doses.

Scheie and Alper [117] treated 11 cases of characteristic herpes zoster ophthalmicus with local cortisone and intravenous corticotropin. All patients had iridocyclitis, and some had glaucoma. Relief of symptoms was prompt, and the results of treatment were good. It is unlikely that corticosteroids had any specific action on the virus, but helped by blocking the response of tissues to the viral agent.

CYSTS AND TUMORS OF THE IRIS AND CILIARY BODY

Cysts.—Among 349 patients with glaucoma and treated with miotics, Gerewitz [118] found 12 eyes with pigment cysts of the pupillary margin. These cysts may disappear spontaneously or may rupture. Cases with large spontaneous cysts of the iris are reported by Heath [119] and by Garron.[120] In Garron's case the cyst resembled a pigmented tumor of the iris and ciliary body. The author points out that almost all reported large spontaneous cysts of the iris and ciliary body begin in the lower temporal quadrant, suggesting a congenital origin. Traumatic cysts of the iris following operation or injury are reported by Holisova and Kavka,[121] Frankenthal,[122] Scheffler,[123] and Rizzuti.[124] Frankenthal treated his case with radiation, while Scheffler and Rizzuti preferred iridectomy, including removal of the entire cyst. Vail [125] treated three such cases successfully with diathermy electrocoagulation, performed with a fine needle passed into the cyst.

Melanomas.—Meisner and Unger [126] describe a case of Recklinghausen's neurofibromatosis of the skin and small intestine associated with pheochromocytoma, retinopathy, and melanophacoma of the irises. Koenig [127] reports the case of a malignant melanoma of the iris and ciliary body which had been treated by irradiation and kept under observation for 20 years. When the patient died, of an unrelated cause, the eye was removed and the diagnosis confirmed by histological examination. No metastases were found. Husain [128] emphasizes the value of gonioscopy in the diagnosis and follow-up of melanomas of the iris base and ciliary body. Sverdlick [129] describes a histologically proved case of malignant melanoma of the iris, apparently arising from a preexisting nevus of the iris. Bangerter [130] successfully excised a malignant melanoma of the iris, and the patient has remained well, without metastases. Another case of this condition is described by Yancey.[131] Lloyd and Ellis [132] report their treatment of an iris tumor by the insertion of two radioactive tantalum wires tied around it. Examination one year later revealed cataract formation, but the tumor appeared quiescent. The lesion was described grossly as a melanoma, but no histological studies were done.

Metastatic Tumors.—Mayer and Ray [133] report a case of carcinoma of the lungs with metastases to the cornea, limbus, iris, and ciliary body. The condition was first diagnosed as granulomatous iritis. Greer [134] describes two cases of metastatic carcinoma of the iris, one originating in the lung, the other from an undetermined site. Trevor-Roper's [135] case had bilateral iris and choroidal metastases. The iris growths were symmetrically placed and were quite separate from the metastatic choroidal tumors. Another iris growth metastatic from the lung is reported by Merritt.[136]

TUMORS OF THE CHOROID

Melanomas.—The behavior of malignant melanoma of the choroid is often unpredictable, and frequently the tumor is present in unusual disguises. Antle [137] presents a case of flat diffuse melanoma of the choroid, which first made itself evident as an acute glaucoma. In the case of Pillet and Baron [138] the lesion was thought to be a hemorrhagic retinal detachment. Enucleation followed an attack of acute glaucoma, and a choroidal tumor was discovered. The case of malignant melanoma of the choroid reported by Biro and Mohay [139] occurred in an atrophic globe 15 months after injury, and the patient died of metastases. Levison [140] reports spontaneous regression of an apparent lung metastasis in a case in which enucleation had been performed because of malignant melanoma. Lindsay [141] describes pigment epithelial cells on the posterior surface of the retina in association with choroidal melanoma. The pigment may vary from week to week, and its presence should suggest the presence of a choroidal tumor in a patient with retinal detachment. Present views on the histogenesis and clinical behavior of malignant melanoma of the choroid are discussed by Moro [142] and by Naim.[143]

MacKova,[144] in a statistical study of 204 cases of malignant melanoma, gives further evidence that approximately only one-half of the patients are cured by enucleation. Recurrences and metastases may be seen even after 10 years. In a study of 60 cases of malignant melanoma of the choroid, Rendahl [145] finds that exenteration of the orbit for a recurrence of the tumor after enucleation, or in the cases in which extraocular extension is already present at the time of enucleation, does not alter the grave prognosis. The author advises against exenteration of the orbit under those conditions, for in these stages distant metastasis has already occurred.

Safar [146] and Jancke [147] report failure in attempting to eradicate a malignant melanoma of the choroid by diathermy coagulation. However, Weve [148] reports success with such treatment for small melanomas of the choroid and choroidal angiomata. The author advocates the use of a weak current applied for a long time.

Metastatic Tumors.—King [149] reports two cases of choroidal metastasis following carcinoma of the breast. Bilateral oophorectomy and adrenalectomy produced great benefit. The case of Scuderi [150] also originated from the breast. Ricketts and associates [151] report the first case of adenoid-cystic bronchial adenoma metastatic to the choroid, and Binder [152] describes an unusual case in which there was the simultaneous appearance of a choroidal sarcoma and a bronchogenic carcinoma. Wagner and Busanny-Caspari,[153] in reporting a rare instance of choroidal metastasis from a chorioepithelioma, state that only nine previous cases have been reported, four occurring in men and five in women.

Diagnostic Procedures.—Andersen [154] describes a special technique of intraocular biopsy. The presumptive tumor is localized with needle aspiration, followed by a trephine biopsy. The author carried out the procedure on 19 cases. The postoperative reaction was slight. The author states that there is no proof that this type of biopsy involves a risk of spreading the tumor but advises its use only in doubtful cases.

There are reports of increased experience in the use of radioactive phosphorus in the detection of intraocular tumors. The technical problems involved in detecting a lesion which is farther from the counter than the maximal range of β-radiation are not yet solved, according to Erbaugh.[155] Bettman and Fellows [156] have devised

an improved scintillating counter. From the experience in a considerable number of cases, Eisenberg [157] and Kennedy and their associates [158] feel that the use of radioactive phosphorus is a useful diagnostic aid in intraocular tumors but that some small tumors of the posterior pole and retinoblastomas do not always give clear-cut results.

Miscellaneous Tumors.—Erdbrink and Harbert [159] report a rather rare leiomyoma of the iris. Clinically the tumor may be indistinguishable from malignant melanoma, especially when lightly pigmented.

Vrabec [160] reports a rare case of malignant epithelioma of the ciliary body arising from the nonpigmented layer of epithelium.

Dufour [161] describes a case in which the diagnosis of malignant melanoma of the choroid was made after exhaustive examinations; yet histologically the tumor was an angioma of the choroid.

MISCELLANEOUS CONDITIONS

Mobus [162] gives extensive case reports of pupillotonia and Adie's syndrome occurring in three young girls. No symptoms other than a certain vegetative lability could be elicited. Brunnschweiler [163] does not believe that the Mecholyl test alone is a reliable aid in the differential diagnosis of Adie's syndrome because it may exert a miotic influence as well as a dilator one in normal persons, although to a slightly less pronounced degree. Cossa, Hemi, and Bailbé [164] describe a case of bilateral Adie syndrome which was mistaken for an Argyll Robertson pupil at first because of its atypical manifestations. The correct diagnosis was made only after repeated examinations had been made, strychnine had been injected subcutaneously, and the collyrium test had been performed.

Apter § reports on his studies of 46 patients with neurosyphilis in which there were 13 cases with unilateral Argyll Robertson pupil. In all 13 cases the miotic, light-rigid pupil was found to be associated with gross abnormalities of the iris, such as absence of the collarette and the presence of fine radial striations. The miotic pupils could be dilated with cocaine and were then capable of constricting in response to light. These findings suggested that the abnormality responsible for the Argyll Robertson pupil may be found in the iris itself, rather than in the central nervous system. Naquin [167] studied a case of true unilateral Argyll Robertson pupil observed seven years after herpes zoster ophthalmicus on the same side. Syphilis was excluded. The author postulated the presence of two efferent pupillary pathways, that for the light reflex being more susceptible to damage by herpes zoster and neurosyphilis.

Bedell [168] described a series of cases with widely dispersed, smoky, yellow-gray areas in the fundus which did not show any pigment. The fresh spots were cloudy and less defined; later they became paler and more sharply demarcated. These spots are quite different from drusen, which are bright and glistening. The author suggests the term "choroidopathy" for the condition, which has not yet been described histologically.

Montanelli [169] reports a case of apparent Doyne's choroiditis occurring in one eye.

Utilizing silver stains, Walter [170] was able to demonstrate brush- or root-like connective tissue structures which penetrate the outer layer of Bruch's membrane from the choriocapillaris of the choroid.

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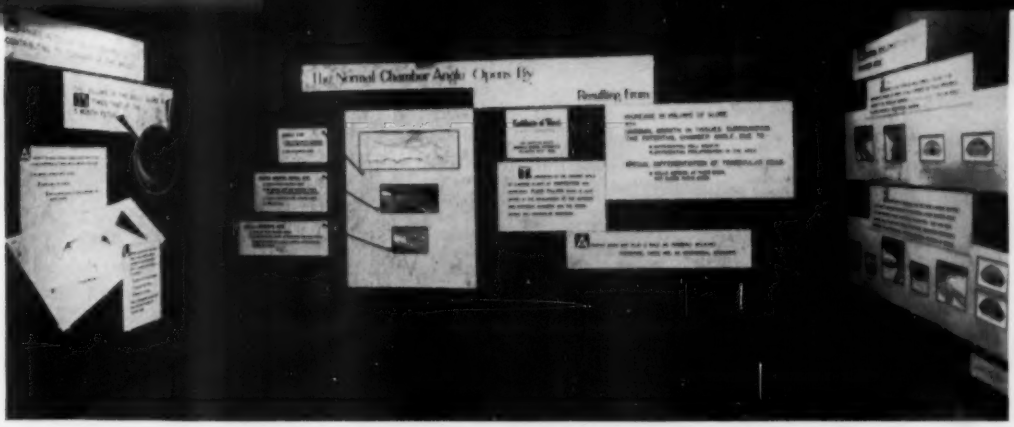

Comprehensive view of exhibits.

Scientific Exhibits

A NEW CONCEPT OF THE DEVELOPMENT OF THE ANGLE OF THE ANTERIOR CHAMBER OF THE HUMAN EYE

HERMANN M. BURIAN, M.D.
ALSON E. BRALEY, M.D.
AND
LEE ALLEN, M.D.
Iowa City

The anterior chamber angle opens by cleavage beginning in the fifth fetal month. The evidence presented disagrees with the previously accepted theory that a measurable amount of tissue must atrophy and be resorbed from between the trabecular and the iris-ciliary body tissues.

Cleavage occurs during a period of extensive growth, the adult eye reaching 35 times the volume of the fifth-month fetal eye. Marked inequality of growth during this period supplies the forces for cleavage by altering the mass and spatial relationships of tissues in the chamber angle region. Differential cell growth and differential proliferation are responsible for the unequal growth.

Differentiation normally progresses simultaneously with the unequal growth, and special differentiation of the trabecular cells contributes a situation favorable to the cleavage in the following respect: As can be seen from study of the normal adult trabecular fibers, certain cells in this tissue are so constituted that they do not adhere to each other along their sides, but only at their ends to form long fibers and stellate junctions. The innermost layer will normally differentiate in the same manner, and only occasional cells might be oriented across the potential chamber angle. Since the cells within the iris root and ciliary body adhere more firmly to

Shown as a scientific exhibit of the Section on Ophthalmology at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 6-10, 1955.

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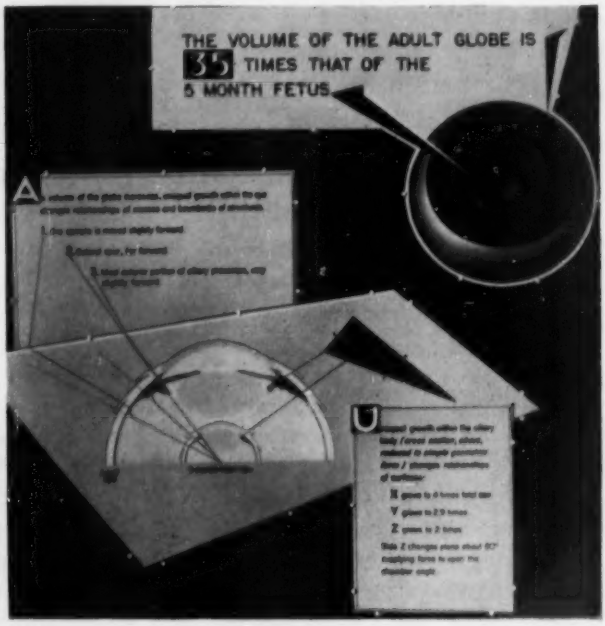
each other, these latter tissues can pull away as a unit from the innermost layer of trabecular fibers where there is little tendency toward adherence.

The layers of cells formerly interpreted as embryonic mesoderm undergoing atrophy and absorption are now seen to be cells under tension due to the occasional cells aligned across the angle. For the most part, these adherences are tenuous and fail under the force of increased tension during further development.

On the new basis, mesodermal remnants, according to the accepted meaning of the term, do not exist. Instead, it is shown that persistent adherence of the iris

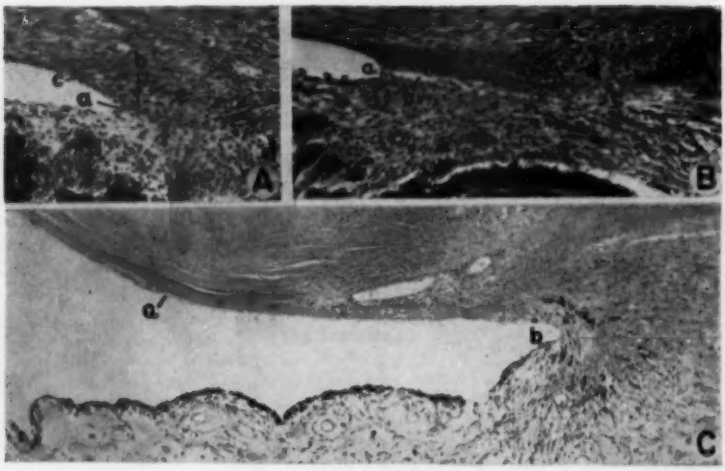


Changes in tissue relationships contributing to cleavage of the angle: As the volume of the globe increases, unequal growth changes relationships of masses and boundaries of structures. The scleral spur and the anterior insertion of the meridional ciliary muscle move noticeably forward and outward from the center of the globe, while the iris root and internal anterior margin of the ciliary body move much less. A comparison of geometrically simplified cross sections of the fifth month fetal and the adult ciliary bodies shows the changed relations of the three major boundary planes. That adjacent to the iris root changes plane about 80°, rotating backward and inward around the scleral spur insertion as a fulcrum, thus pulling the chamber angle open.

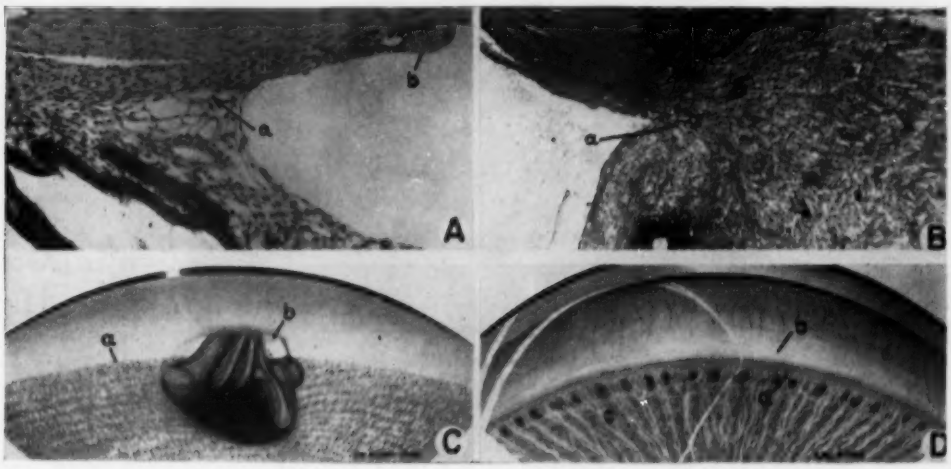
root to the trabecular tissue can give the gonioscopic appearance formerly attributed to embryonic mesodermal remnants. Poor differentiation and organization in the trabecular region can be seen as the most likely cause of the persistent adherence. It may in itself, or through the adherence, or both, cause or contribute to developmental glaucoma with which both are often associated.

Other tissues in the chamber angle also formerly thought to be remnants of an atrophic process are shown to develop from groups of excessive cells. These appear to be atavistic and relate to the ring of Schwalbe and pectinate ligaments of lower mammals. Such groups are found as early as the 91 mm. embryonic stage. In all embryonic eyes they appear in the same percentage as they are seen in adult eyes by clinical or anatomic study.

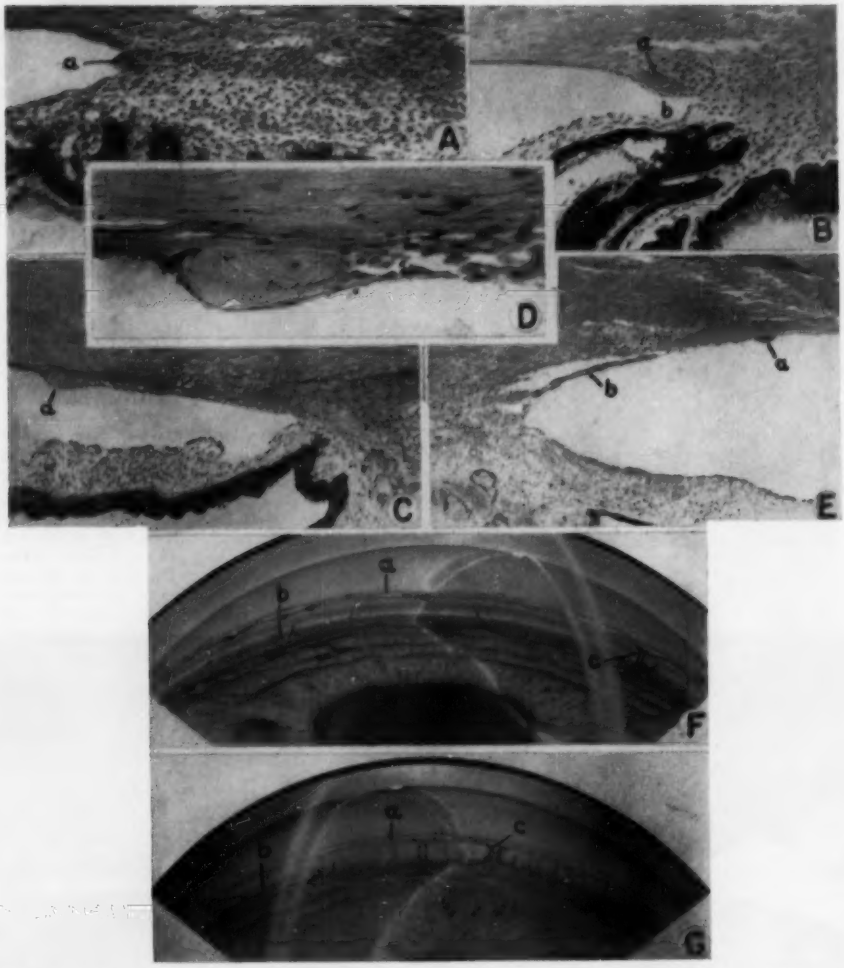
The persistent adherence and poor differentiation can occur together with pectinate ligament elements, in which cases the gonioscopic and histologic pictures can be quite complex.



Size increase, differentiation, and cleavage are seen: *A*, 120 mm. embryo eye; *a*, apex of fetal chamber angle; *b*, large granular nuclei of developing trabecular cells; *c*, *d*, *e*, *f*, outline area of differentiating trabecular tissue. *B*, fifth-month fetal eye; *a*, apex of fetal chamber angle; *b*, developing cleft with trabecular tissue above and iris-ciliary body tissue below; *c*, potential apex of adult angle; *d*, scleral spur. *C*, adult chamber angle; *a*, edge of Descemet's membrane (no prominent border ring of Schwalbe is present); *b*, apex of adult chamber angle.



Abnormal development seen in developmental glaucoma with faulty cell differentiation and persistent adherence of the root of the iris to the trabecular tissue (incomplete cleavage): *A*, fetal eye (some time after the fifth month); *a*, persistent adherence; *b*, prominent ring of Schwalbe. *B*, eye of child with developmental glaucoma; *a*, persistent adherence; *b*, disorganized trabecular tissue. *C*, gonioscopic view of fellow eye to that shown in *B*; *a*, persistent adherence; *b*, trephine opening, ciliary processes incarcerated, and peripheral iridectomy. *D*, gonioscopic view of eye of child with developmental glaucoma; *a*, persistent adherence; *b*, indistinct anterior boundary of trabecular tissue, probably indicating poor differentiation; *c*, iris atrophy.



Abnormal development with prominent anterior border ring of Schwalbe and pectinate ligament features: *A*, chamber angle 91 mm. embryo; *a*, cells already forming prominent ring of Schwalbe and possibly pectinate ligament strand, excessive to requirements of normal human eye. Blue-staining collagen fibers are clearly seen in Mallory stain. *B*, fetal eye (courtesy of R. N. Shaffer and A. E. Maumenee); *a*, prominent ring of Schwalbe; *b*, clear-cut cleavage with imprint of ring in iris root. *C*, adult eye; *a*, prominent ring of Schwalbe. *D*, ring of Schwalbe in *C* viewed under high power. *E*, adult eye; *a*, prominent ring of Schwalbe; *b*, pectinate ligament strand. *E*, gonioscopic view of adult eye without glaucoma; *a*, prominent ring of Schwalbe; *b*, minimal persistent adherence; *c*, pectinate ligament strands. *G*, gonioscopic view of adult eye with glaucoma; *a*, prominent ring of Schwalbe; *b*, extensive persistent adherence; *c*, pectinate ligament strands.

Correspondence

CONGENITAL ALACRIMIA

To the Editor:—In Dr. Dunnington's comprehensive article on "Congenital Alacrima," on page 925 of the December, 1954, issue of the ARCHIVES, the term "alacrima" was proposed as a substitute for the previously used expression "alacrimia."

Prof. Werner Jaeger, Ph.D., Litt. D., Head of the Institute for Classical Studies at Harvard University, was kind enough to discuss this problem upon my request and to permit publication of his opinion. I am quoting from his letter what might be of interest to the readers of these ARCHIVES.

"Alacrimia . . . is one of those hybrids that are composed of a Latin word (*lacrima*) and the Greek alpha privativum, indicating the absence of . . . tears. . . . If, however, we may take for granted that such formations must exist for practical reasons and do exist already in great numbers, the word *alacrimia* is unobjectionable because the "i" should be there in order to indicate that this is a state or disposition, a kind of noun that ends in "-ia." . . . The word *alacrima* is a progress from bad to worse and certainly cannot indicate a state or disposition of the eyes, which would require "-ia" as ending."

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DALLOS CONTACT LENSES

To the Editor:—I trust you will afford me space to comment on certain inaccuracies in the article by Drs. Zekman and Krimmer, published in the October, 1955, issue of the ARCHIVES.

They state: "The Dallos glass lens had many disadvantages, chief of which were difficulty in manufacture, excessive weight, breakage, and poor optical qualities." I shall deal with these statements separately.

"Many disadvantages, chief of which . . .": This turn of phrase is singularly out of place in a serious scientific contribution. Can the authors enumerate the lesser disadvantages which, by inference, they have found?

"Difficulty in manufacture": Of course manufacture is difficult; manufacture of any article is difficult if great accuracy is required. But there is with these lenses no manufacturing difficulty which cannot be and has not been overcome by competent craftsmen. Is it suggested that a patient should be supplied with an inferior contact lens merely because it is cheap and easy to make?

"Excessive weight": In excess of what? Is a satisfactory weight to be arrived at by reference to the lightest lens that can be made irrespective of tolerance? Or should the patient's tolerance be the prime factor?

"Breakage": In thirty years' experience, I have yet to hear of a glass contact lens being broken in the eye. If the reference is to breakage outside the eye, then I would state that accidents of this kind are in my experience infrequent and are of much less consequence than the speedy deterioration found with plastic lenses.

"Poor optical qualities": I am not certain whether this libelous statement arises from Drs. Zekman and Krimmer being insufficiently experienced to judge such matters or whether they have never so much as seen what they profess to judge.

Your authors hold the surprising belief that fluidless lenses did not appear until the Tuohy corneal lens, in 1948. They might care to consult some of my papers, e. g., "Über Haftgläser und Kontaktschalen" (*Klin. Monatsbl. Augenh.* **91**:640, 1933), or "The Individual Fitting of Contact Lenses" (*Tr. Soc. Ophth. U. Kingdom* **57**:609, 1938), or "Sattler's Veil" (*Brit. J. Ophth.* **30**:607, 1946), where ventilated contact lenses are described, admittedly, for the first time.

JOSEPH DALLOS, M.D.
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To the Editor:—It was not our intent in any manner whatever to disparage or detract from the pioneering of Dr. Joseph Dallos in the development of contact lenses. The authors are well familiar with his work of the last 30 years.

We appreciate the references offered by Dr. Dallos as admittedly identifying him with the first use of ventilated contact lenses. In the article appearing in the *Klinische Monatsblätter für Augenheilkunde*, he describes the construction of his lens and the results of its use in 12 patients, 8 of whom had keratoconus, and for these he does illustrate slight improvement in visual acuity; however, with only one exception, the patients could tolerate the lens no more than two to four hours.

Tolerance, from the standpoint of both the patient's feeling of comfort and the actual ability of the eye tissues to tolerate the lens, is paramount. Weight influences this tolerance in both meanings of the word. Tolerance of the eye to the lens can be influenced by weight alone both with respect to comfort of wearing and the maintenance of proper positioning of the lens; excessive weight can cause the lens to drop in wearing.

Our reference to the "poor" optical qualities of the Dallos lens is incorrect—an inadvertence in composition, made when compiling our notes. For this we apologize. There have appeared in the literature, however, certain criticisms of the Dallos contact lens, and these objections have been borne out in our limited experience, limited only because the Dallos lenses have not been available in this country for trial.

On page 160 of the first edition of the text by Theodore Obrig, entitled "Contact Lenses," the following can be found: "The Dallos molded contact lens is constructed entirely of transparent glass. It is usually made as large as the casting and the comfort of the patient will permit, an approximate average size of 22 x 25 mm. It has a corneal portion which is optically ground and polished to prescription. When it is properly fitted, it can be worn over useful periods of time which naturally vary with each patient. Its weight, the difficulty in making alterations in the semi-finished lenses, the time consumed in doing so, and the possibility of breakage are the only possible features which can be criticized." It should be mentioned that Obrig was not referring to keratoconus patients, who were our immediate interest.

When an attempt was made to survey four types of lenses for use for Army personnel, as reported by Dr. James L. McGraw of Syracuse, N. Y., and Dr. J. M. Enoch (Contact Lenses: An Evaluation Study, AMRL Project No. 6-64-12-028, Report No. 99, Army Medical Research Laboratory, Fort Knox, Ky., Oct. 10, 1952), the Dallos glass ventilated contact lens proved complex to fit. It was "easily broken"; it was found that "ocular irritants result in discomfort," and "mucus frequently plugs vent." McGraw and Enoch found the Dallos lens otherwise of superior quality, and the Lacrilens, which is plastic, to be comparable.

It is willingly acknowledged that Dr. Dallos is a master craftsman in the grinding and fitting of his type of lens. Unfortunately, to our knowledge, his lenses are not available in America, where no craftsman has been able to duplicate his work in glass. Fabrication is always difficult, but it should be possible of accomplishment in skilled hands anywhere if the product is to have universal practicability and application.

Because the Dallos lens has not been accessible, our experience has been limited. Insofar as others have reported on their experiences and to the extent to which we have observed the Dallos lens, we find the corneal plastic lens is safer from the standpoint of breakage in handling. We have not heard that the lens ever broke in the eye, but that is not to say that it could not happen; the potential exists, and even once would be disastrous.

We are not aware of "deterioration," "speedy" or otherwise, of the plastic lens. No one working in plastic has reported this consequence.

It is regrettable that any personal aspersion was assumed. None was intended.

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News and Comment

ANNOUNCEMENTS

National Society for the Prevention of Blindness: Sight-Saving Conference.—The 1956 Sight-Saving Conference of the National Society for the Prevention of Blindness will be held March 26, 27, and 28 at the Palmer House in Chicago, it has been announced by the National Society for the Prevention of Blindness, conference sponsor.

Reports of new research into the causes of the blinding eye diseases will be made by outstanding ophthalmological investigators during the three-day sessions. Other highlights include the presentation of new techniques and procedures in various phases of sight conservation work in the fields of medicine, education, nursing, social work, and safety. Many interesting related exhibits will be on display.

Several hundred delegates from all parts of the United States are expected at the three-day conference.

Individual reservations should be made directly with the Palmer House at Chicago. Advance programs may be obtained by writing to the National Society for the Prevention of Blindness, 1790 Broadway, New York 19.

Course in Ophthalmic Plastic Surgery.—A course covering the essentials of ophthalmic plastic surgery for the practicing ophthalmologist is being offered by the Post-Graduate Medical School, a unit of New York University-Bellevue Medical Center.

Under the direction of Dr. Sidney A. Fox, sessions will be held from 2 to 5 p. m. from April 2 through 6, 1956. By lecture and demonstration special emphasis will be laid upon the commoner fundamental procedures peculiar to lid surgery. These include such minor plastic surgery as tarsorrhaphy, canthoplasty, excision and repair of lid margin lesions, as well as the usual classical operations for the correction of ptosis, ectropion, socket lesions, and others. The steps in the various techniques are systematically outlined and the choice of the suitable technique for various clinical conditions is considered.

The tuition for the course is $75.00, and applications may be sent to the Office of the Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16.

American Board of Ophthalmology: Changes in Requirements (applicable to applicants who start residencies in ophthalmology after Dec. 31, 1956).—Candidates who have completed three years of formal ophthalmological training (residency and basic science courses) may apply for the written qualifying test after completion of 12 months of practice or 12 months of institutional work, a total of 48 months. All other persons (with less formal training) may apply for the written test after 60 months in ophthalmology or 72 months of combined ophthalmology and otolaryngology. A basic course is recognized as equivalent in time to residency training. All time requirements must be completed by the date of the written test.

Basic Course in Orthoptics for Technicians.—This course, sponsored by the American Orthoptic Council, will be held in the department of ophthalmology, University Hospitals, Iowa City, from June 20 through Aug. 11, 1956. As usual, there will be didactic lectures and practical demonstrations, given by an outstanding faculty. Further information, as well as application blanks, may be obtained from Hermann M. Burian, M.D., University Hospitals, Iowa City.

SOCIETY NEWS

Irish Ophthalmological Society.—The Irish Ophthalmological Society will hold its annual meeting in Dublin on May 10, 11, and 12, 1956. The Montgomery Lecture will be delivered by Dr. Moacyr E. Alvaro (Brazil) at 5 o'clock on Thursday, May 10, in Trinity College, Dublin.

Pacific Coast Oto-Ophthalmological Society.—The 40th Annual Meeting of the Pacific Coast Oto-Ophthalmological Society will take place in Phoenix, Ariz., April 15-19, 1956.

Guest of honor at the meeting is Horace G. Merrill, M.D., of San Diego, Calif., and the guest speaker is A. C. Furstenberg, M.D., dean of the Medical School and professor of otolaryngology, University of Michigan. There will be scientific and motion picture programs in otolaryngology and in ophthalmology throughout the week and instruction courses in both specialties on Tuesday.

President of the society is Lester T. Jones, M.D., of Portland, Ore., and John F. Tolan, M.D., of Seattle, is secretary-treasurer.

Association for Research in Ophthalmology, Midwest Section.—The scientific session of the Midwest Section of the Association for Research in Ophthalmology will be held in Chicago on March 17, 1956, Room 407, Commerce School, Northwestern University, 321 E. Chicago Ave. The session begins at 9:00 a. m. and 2:00 p. m. Lunch at cafeteria at Abbott Hall, across the street. The program follows:

Julia T. Apter, Manteno, Ill.: Effect of Hallucinogenic Drugs on the Electroretinogram Studies on the Autonomic Innervation of the Iris

S. B. Goren and A. C. Krause, Chicago: Oxygen in the Vitreous Humor in Anoxia and Hyperoxia

I. Gersh, Chicago: Electron Microscopy of Ocular Tissues

K. L. Chow, Chicago: Disuse and Retrograde Degeneration of Retinal Ganglionic Cell

E. S. Guzman Barron, Chicago: On the Mechanism of Oxygen Poisoning

N. P. Arribas and T. F. Schlaegel Jr., Indianapolis: Experimental Toxoplasmosis in the Rabbit

P. T. White and T. F. Schlaegel Jr., Indianapolis: Results of Photic Driving on the Electroencephalograms of Patients with Suppression Amblyopia

N. Kent and T. F. Schlaegel Jr., Indianapolis: Selective Perception in Hysterical Amblyopia

P. A. Cibis, M. Constant, and G. Pribyl, St. Louis: Ocular Lesions Produced by Iodoacetate

R. E. Christensen and B. Becker, St. Louis: Effect of β-Hypophamine on Intraocular Pressure and Aqueous Flow in Human Eyes

M. A. Constant and B. Becker, St. Louis: Experimental Tonography: II. Effect of Various Compounds on the Intraocular Pressure of the Rabbit

R. D. Richards, Iowa City: Histologic Changes in Radiation Cataracts in Mice

M. Hobson Rice, Iowa City: Familial Occurrence of Developmental Anomalies of Cornea, Iris, and Chamber Angle with Visible Region of Schlemm's Canal

C. Matta, Iowa City: The Skin Test for Moniliasis

P. J. Hauser, Iowa City: Studies on the Fixation Pattern in Amblyopia ex Anopsia

F. C. Blodi, Iowa City: Influence of Newer Ganglioplegics on the Eye

M. Armaly, Iowa City: Comparison of Bulbar Pressure Test and Tonography

F. W. Newell and T. Sheftel, Chicago: Studies Concerning the Ocular Hypertensive Reaction Following Paracentesis

G. J. Wyman, Peoria, Ill.: Use of Versene in Removal of Rust in the Cornea

CORRECTION

In the notice of the meeting of the American College of Surgeons, held in Philadelphia in February, 1956, the name of Dr. Harold G. Scheie was incorrectly inserted as Chairman, Section on Ophthalmology, College of Physicians of Philadelphia. Dr. I. S. Tassman is Chairman of the Section.

Books

Our Wonderful Eyes. By John Perry, with foreword by Dr. George Wald. Price, $2.75. Pp. 158, including index. Whittlesey House, McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1955.

Dr. George Wald, who wrote the foreword to this delightful little book, states in his foreword, "Mr. Perry has given us an extraordinarily lively and informative introduction to the eye and vision in this little book. As a teacher I admire its clarity and skill of presentation. As a scientist I enjoy the ingenuity with which Mr. Perry leads the reader to explore the subject for himself, in clear and simple experiments which go directly to the mark and require no special apparatus or skills."

Mr. Perry, who has lived in Washington since 1939, is a consultant on visual presentation and human relations and has worked with industries, professional societies, and federal agencies, including the National Federation of the Blind. He is extraordinarily well versed in the physiology of the eye, and has the happy facility of describing complex phenomena in relatively simple terms, and, what is even more remarkable, without making any gross misstatements. His presentation of the whole of vision is quite accurate and contains much information that even well-trained ophthalmologists are not usually familiar with. The book is avowedly for the lay person, and, in addition to chapters describing the way the eyes function, many practical things are given consideration, for example, taking care of your eyes, the difference between an ophthalmologist and an optometrist, and a chapter on what it is like to be blind.

This book can be recommended to any intelligent layman. It would be very helpful if it were included in all courses in school science. Particular praise goes to Jean Bendick, who did the illustrations.

Essentials of Biological and Medical Physics. By Ralph W. Stacy, Ph.D.; David T. Williams, Ph.D.; Ralph E. Warden, M.D., and Rex O. McMorris, M.D. Price, $8.50. Pp. 586, with index and numerous illustrations, not listed numerically. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 16, 1955.

The chief interests for ophthalmologists in this book are the chapters on the biophysical studies of light. These topics include light and its biological effects, light used as a therapeutic tool, the biophysics of the visual processes, geometric optics in vision, the physical basis of microscopy, optical activity of biological material, and the physical nature of animal light. All these chapters are well done and present the material from the point of view of the physicist. This is of particular interest in the biophysics of the visual processes. There has necessarily been so much condensation of the material that only one who is already familiar with the general subject would have much rapport with this book. For those who wish to go further afield into medical physics the book covers the whole field of biophysics, including mechanical biophysical systems, heat and thermodynamics in life, bioacoustics, gas physics in biology, fluid-flow systems in biology, electrical systems in biology, nuclear physics in biology, and chapters on fundamental concepts and theoretical biophysics. Obviously, much of the treatment is mathematical and can be appreciated only by those familiar with the calculus.

A Textbook for Diploma Students. By Patrick D. Trevor-Roper. Price, $15. Pp. 656, including index. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1955.

The purpose of this text is primarily to prepare students in both the basic sciences and the clinical fields of ophthalmology. It applies in particular to those students who are about to take the London "Diploma in Ophthalmology," which

corresponds to the examinations given by the American Board of Ophthalmology. The selection of material is good, and, as is usual with almost all English texts, the writing is a model of style. Clarity of expression must depend upon clarity of thought, and those who can express themselves well probably think clearly. The ease with which a student can assimilate knowledge from a book is in large measure determined by the style of presentation. This is particularly true in subjects where reasoning processes must be applied, as in the complex phenomena of strabismus. It is a vast field, and the author has succeeded in bringing all the material up to date. The illustrations, which include many colored plates, are excellent. This book is one of the best texts on ophthalmology which has appeared for many years. It should prove to be very popular.

Medical Research—A Midcentury Survey. Published for the American Foundation, 565 Fifth Ave., New York 17. Price, $15. Pp. 740, Little, Brown & Company, 34 Beacon St., Boston 6, 1955.

The American Foundation was established by Edward Bok in 1924 for the purpose of critically reviewing problems related to the public welfare. In the past this Foundation has gathered and publicized impartial analyses of such different problems as the role in international relations of the judicial settlements of international disputes, the progressive codification of international law, the relations of record between the United States and the Soviet Union, the principles involved in ways of distributing and paying for medical care, and, finally, in the present report, the more fundamental problem of the maintenance of high standards of medical education insofar as it is affected by medical research.

In 1937 the American Foundation published two volumes of an analysis by physicians of current problems in medical education and medical practice. They admit that as a result of this study there emerged a conviction that it was useless to discuss the administrative problems of distributing medical care and the economic problems of paying for it until the more fundamental problem was solved of insuring a sufficient number of trained physicians, capable of providing the type of medical care which could justify such elaborate plans. In retrospect, therefore, it seems that these present volumes should have preceded the others. It is fortunate, and particularly so at this time, that the Foundation turned its energies to the subject of basic research, which is fundamental to all problems of medical progress, and which at this particular time needs the attention of the best minds in medicine, for it seems to be true that, as the uneasy pressures of a cold war have settled upon us, too much attention has been paid, in medicine as elsewhere, to research which has an immediate application, and basic research, that is, investigations having no immediate foreseeable practical use, has almost disappeared from the scene.

The appearance of these two volumes is particularly important for ophthalmology at this time. Over the past thirty years funds for basic research in ophthalmological problems have dwindled until they have become almost nonexistent. The foundations which used to supply grants-in-aid for specific problems of basic anatomy, embryology, physiology, and chemistry in the ophthalmological field have turned their attention and their support elsewhere. Their place has been taken by the National Institute of Neurological Diseases and Blindness of the Institutes of Health, which is a Federal agency. In the several years which this has functioned, considerable, but still inadequate, funds have been provided for ophthalmological problems. The majority of these have been of an immediately practical nature. The purse strings of the committee are held by Congress, and it is extremely difficult to persuade Congress to make funds available for anything which does not have an immediately practical return. Each year, when more funds are requested, Congress wants to know just what was accomplished with the money appropriated in the previous year. If, as, fortunately, it can occasionally be shown, as in the case with the money appropriated for research in retrolental fibroplasia, the expenditure of the funds has resulted in a definite answer to a serious problem and, as a direct result, the public health has benefited, Congress will feel quite happy to make further appropriations. It is quite another thing to tell Congress

that the money has been spent in widening our horizons of knowledge on corneal metabolism, or on solving the problem of where the a-wave in the ERG arises, merely because these questions have no immediate practical value; yet, as everyone knows, it is this type of research, and this type alone, which eventually enables us to make the type of studies which solved the problem of retrolental fibroplasia. It has been repeatedly stressed by those who know that it is almost useless for a research worker to appear before Congress and try to impress this august body with the need for basic research. To the average Congressman the investigator making the appeal is biased. It is quite another thing when an independent, completely unbiased organization, such as the American Foundation, makes a thorough study of the situation and comes up with two volumes leading to the conclusion that basic research in medicine must be given more support, and at this time. These two volumes may not even be read by the Congressmen who parcel out these appropriations, but their very existence will go a long way toward persuading the members of Congress that this is a real problem, and that it is their responsibility to meet it. Ophthalmology, as well as other branches of medicine, therefore, will welcome the appearance of these two volumes, and will be grateful to the Foundation and its committee of consultants who did all the spade work to make them possible.

It would be impossible to cover the subject material adequately in a review. Volume I deals with the problem in its over-all aspects, including current trends and current problems, and research agencies which are engaged in meeting these problems. Of chief interest is the section which reports the research carried out in the past few years in the leading medical schools of the country, and reported by each school. Ophthalmology is well represented.

Volume II contains a report on nine, as yet unsolved clinical problems and reviews the current trends in fundamental research now being pursued in these conditions. It is quite evident that these volumes could never have been compiled without one driving spirit. Esther Everett Lape, who is the active member in charge of the American Foundation, has written the introductory remarks which tie the work together, and has been largely responsible for the careful selection and compilation of material. As Dr. Thomas Parran, the former Surgeon General, U. S. Public Health Service, commented, this is "a monumental task of reviewing an extensive literature, extracting the most pertinent ideas, and synthesizing them into a fascinating text."

The Prevention of Disease in Everyday Practice. By Isador Givner and Maurice Bruger. Price, $20. Pp. 964, including index, with 50 test illustrations, with frontispiece in cover. C. V. Mosby Company, 3207 Washington Blvd., St. Louis, 1955.

The practice, as well as the theory, of preventive medicine has in the past been largely collective. Preventive medicine has been practically synonymous with the term "public health" as it is used today. However, now that many of the public health problems, such as the obliteration of epidemics that once decimated whole communities, have been largely controlled, and now that disease processes which formerly took their toll of large numbers of persons have been relegated to history, it is time that physicians begin to pay more attention to preventive medicine on an individual basis, and to give thought not only how to treat persons with disease but how to prevent them from becoming diseased.

This book is a series of thirty-seven essays by forty-seven practitioners of medicine relating how the general practitioner may try to keep his patients free of certain disease processes. The prevention of disease, as it is used here, also includes the prevention of complications of disease, which, as the authors state, is an integral phase of preventive medicine. Practically the whole field of medicine and surgery has been covered. In Chapter 29, entitled "Preventive Ophthalmology," Dr. Givner discusses blindness in the U. S. and how each of the medical specialties, including ophthalmology, can cut down the appalling number of totally or partially blind people. As Dr. Givner states, there are at present 316,000 persons in the U. S. who are completely blind, 25,000 persons whose visual acuity is reduced to

20/200 or less each year, and at least 1,000,000 blind in one eye. No adequate estimate can be made of how many people have some serious visual loss in one or both eyes. For the internist, syphilis, glaucoma, and diabetes are discussed. The anesthetists are warned about exerting external pressure on an eye of patients whose blood pressure is lowered by shock or anesthesia. Dermatologists are instructed in Stevens-Johnson disease and atopic dermatitis; obstetricians, on congenital anomalies and prophylaxis of the newborn, and retrolental fibroplasia. The chief message addressed to pediatricians is strabismus. Ophthalmologists are given some general practical points in a variety of fields. Paul Chandler discusses the prevention of blindness in glaucoma and its prophylaxis; Byron Smith, the preventive aspects of plastic surgery about the orbital region, as to the preliminary tests before surgery is undertaken, the technical details of plastic surgery, and postoperative management. John MacLean discusses the prevention of complications in cataract surgery, and, finally, C. L. Schepens offers some suggestions for preventing complications in the surgery of retinal detachment.

All of these chapters are well written and are a valuable contribution to our literature. In addition to that, the ophthalmologist will find considerable of interest and of practical value in a number of other chapters on nonophthalmological subjects.

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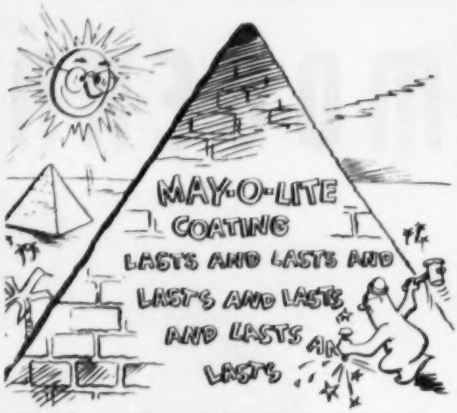

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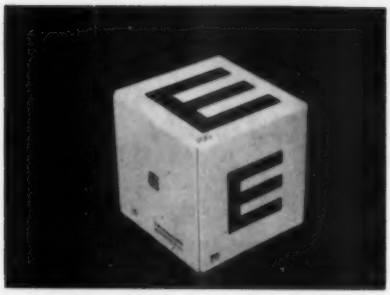

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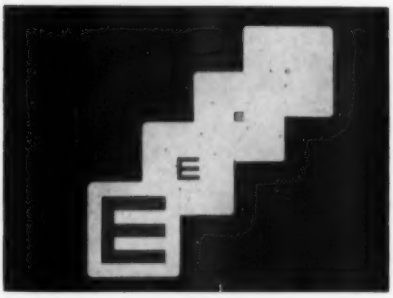

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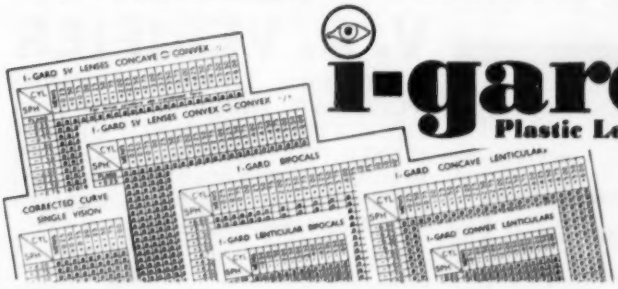

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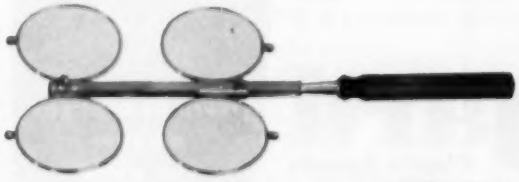

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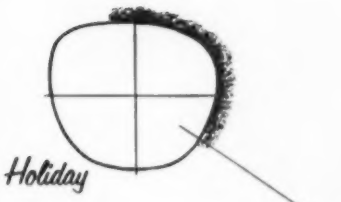

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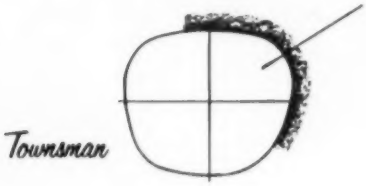

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